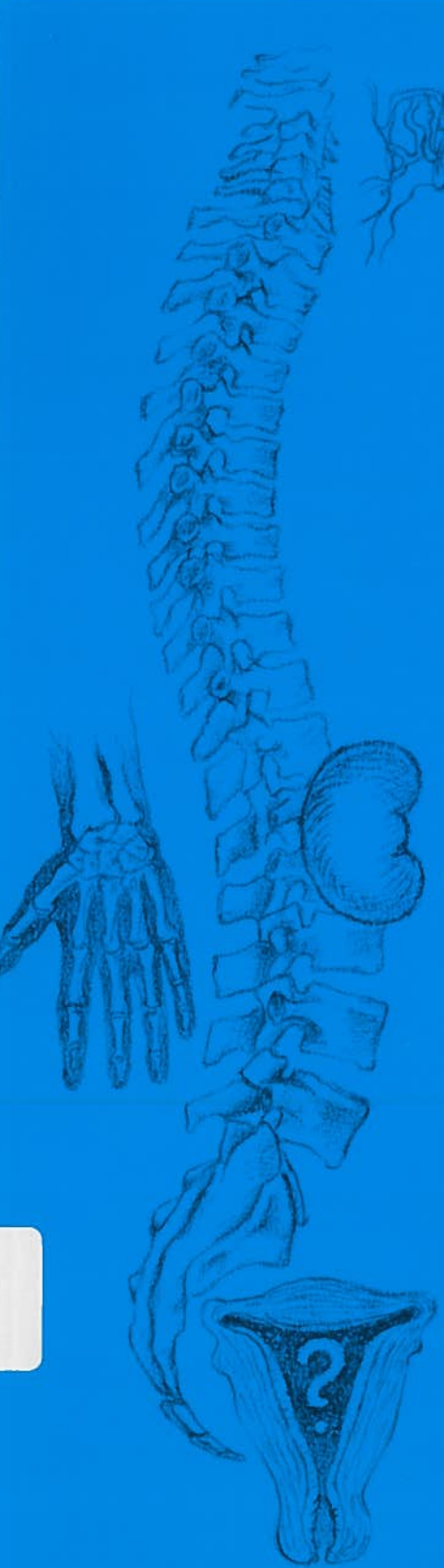
The Mayer-Rokitansky-Küster-Hauser Syndrome. A descriptive study of radiological and physical signs.

Strübbe, Ernst Hendrik



THE MAYER-ROKITANSKY-KÜSTER-HAUSER SYNDROME

A descriptive study of radiological and physical signs

E. H. Strübbe

THE MAYER – ROKITANSKY – KÜSTER – HAUSER SYNDROME

A descriptive study of radiological- and physical signs

STELLINGEN

behorende bij het proefschrift: „The Mayer-Rokitansky-Küster-Hauser syndrome", E.H. Strübbe

1. De atypische vorm van het Mayer-Rokitansky-Küster-Hauser syndroom dient middels laparoscopie onderscheiden te worden van de typische vorm.
2. Audiologisch onderzoek dient plaats te vinden bij patiënten met de atypische vorm van het Mayer-Rokitansky-Küster-Hauser syndroom.
3. Met congenitale afwijkingen van de tractus uropoieticus behoeft bij de typische vorm van het Mayer-Rokitansky-Küster-Hauser syndroom geen rekening gehouden te worden.
4. Alle vormen van het Klippel-Feil syndroom kunnen worden waargenomen bij de atypische vorm van het Mayer-Rokitansky-Küster-Hauser syndroom.
5. De atypische vorm van het MRKH syndroom is als apart syndroom te beschouwen, met de MURCS associatie als onderdeel daarvan.
6. De term MRKH syndroom zou uitsluitend gereserveerd moeten blijven voor de typische vorm.
7. De term „basic femaleness" heeft niets met feminisme te maken, maar geeft een physiologisch ontwikkelingsproces weer gedurende de eerste 7 zwangerschapsweken.
8. Hoewel MRI het onderzoek van keuze is bij het vermoeden van een brughoekproces, is differentiatie tussen acusticus neurinoom en het haemangioom van de inwendige gehoorgang niet mogelijk.
   (Cremers C.W.R.J. et al, Am. J. of Otology 1991; vol. 12, 5: 370-373).
9. Het aantonen van een „sinustract" middels CT-onderzoek bij een lucente botafwijking is zeer suspect voor osteomyelitis.
10. Het is een verheugend feit voor de gezelligheidsdrinkers dat recentelijk onderzoek heeft aangetoond dat de sterfte door cardiovasculaire ziekte lager is bij 1 à 2 alcoholische consumpties per dag dan bij geheelonthouders, terwijl de kans aan andere ziekten te overlijden hierbij nauwelijks is gestegen.
    (Klatsky, A.L. Am. J. Cardiol. 1990; 66: 1237-1242).
11. Door de diversiteit van de tropische planten-en dierenwereld zijn er vele geneesmiddelen te vinden. Dit grote genenreservoir dient op grote schaal beschermd te worden.
12. Het alfabetisch noemen van referenties in wetenschappelijke verhandelingen is praktischer voor zowel de lezer als de schrijver van publicaties in vergelijking met de voorgeschreven volgorde van vermelding in de tekst.
13. In de term „ontspanningspolitiek", gebruikt voor de toenadering tussen West- en Oost-Europa, kunnen de eerste 3 letters beter verdwijnen.
14. Het schrijven van een proefschrift en Zwitserland hebben de bergen en dalen gemeen.

RIJKSUNIVERSITEIT GRONINGEN

THE MAYER-ROKITANSKY-KÜSTER-HAUSER SYNDROME

A descriptive study of radiological- and physical signs

PROEFSCHRIFT

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geboren op 19 maart 1953
te de Bilt.

1993
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Promotores: Prof. Dr. C.J.P. Thijn
Prof. Dr. R. Rolland

Referenten: Dr. W.N.P. Willemsen
Dr. C.W.R.J. Cremers

Aan

Marga
Gijs, Saskia

VOORWOORD

Dit proefschrift kwam tot stand in samenwerking met de Kliniek voor Gynaecologie en Obstetrie, Academisch Ziekenhuis Nijmegen (hoofd: Prof. dr R. Rolland), de Kliniek voor Keel-Neus-Oorheelkunde, Academisch Ziekenhuis Nijmegen (hoofd: Prof. dr P. van den Broek), de afdeling Radiodiagnostiek, Academisch Ziekenhuis Nijmegen (hoofd: Prof. Dr. J.H.J. Ruijs) en de afdeling Radiodiagnostiek, Academisch Ziekenhuis Groningen (hoofd: Prof. dr C.J.P. Thijn).
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Chapter I

INTRODUCTION

I.1 Historical Perspective

The Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, defined as the congenital absence of uterus and upper vagina, is a well-known entity (1-4). Many reports have described the syndrome and associated anomalies, most of them dealing with renal or spinal abnormalities (1-3, 5-8). However, most reports described the therapeutic consequences only or are presented as case reports (1-4, 7, 9-11). Little attention has been paid to the atypical form of the MRKH syndrome. A suggestion to discriminate between the typical and the atypical form based on more serious extragenital abnormalities, especially renal and spinal abnormalities, was made by Schmid-Tannwald & Hauser, Heidenreich and Willemsen (11-13). In addition Schmid-Tannwald & Hauser (12) and Willemsen & Dony (11) mentioned an anatomical difference with respect to the uterine bud- and fallopian tube development. They described the atypical form as differing from the typical form by: asymmetrical uterine remnants (aplasia of one or both muscular buds, and when both muscular buds were found, one muscular bud was larger with respect to the contralateral one) and abnormalities of the fallopian tubes (hypoplasia or aplasia of one or both tubes). The typical form of the syndrome was characterized by symmetrical uterine remnants (the muscular buds) and normal fallopian tubes.

In 1979 Duncan described the MURCS association: Müllerian duct agenesis (MU), Renal agenesis/ectopia (R), Cervical somite dysplasia (CS), as being a separate entity (14).

Since Duncans publication, some of the patients mentioned in the literature were recognized to have this entity whereas others were not (2, 5, 10, 12, 15-17). Some reports mentioned upper extremity abnormalities in association with the MRKH syndrome, others mentioned deafness (1, 2, 8, 10, 13, 14, 18, 19). However, it remains unclear which of these lesions are relevant in the MRKH syndrome, especially with respect to the atypical form.

I.2 Purpose of the study

The objective of the study was to determine the value of additional examinations in patients with the MRKH syndrome and to decide if a subdivision of the syndrome into the typical and the atypical form makes sense. The MURCS association was studied to find out whether it is a separate entity or not.

To rubricate the MRKH syndrome and to study the associated anomalies systematically, particularly with respect to the typical and atypical group, the

following items were studied in a representative patientgroup known to have the MRKH syndrome:

- Hand abnormalities (N=40)
- Spinal abnormalities (N=96)
- Renal anomalies and ovarian desease (N=91)
- Hearing loss (N=51)
- MURCS association (N=100)

The results of the studies have been published and are here presented as chapter IV-VIII.

I.3 Questions

Question 1:
Is subdivision of the MRKH syndrome into the typical and atypical form of value?

Question 2:
Are upper extremity abnormalities, particularly those of the hand, to be expected in patients with the MRKH syndrome?

Question 3:
Which types of renal and spinal abnormalities are to be expected in the typical- and atypical form of the MRKH syndrome respectively?

Question 4:
Is additional audiometrical screening of value in patients with the MRKH syndrome?

Question 5:
Is the MURCS association a separate entity?

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Chapter II

GYNECOLOGIC ASPECTS

II.1 Clinical features

The Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is not an uncommon cause of primary amenorrhea (1-4). Most patients with the MRKH syndrome are seen after the time of expected menarche because of primary amenorrhea. Some patients are seen because of sterility or dyspareunea (1, 5-6). Cyclic abdominal pain is unusual and caused by the presence of functioning endometrium (1, 3). Patients with the MRKH syndrome will have normal female secondary sex characteristics and a normal ovarian function (1-6). The karyotype is that of a normal 46,XX woman (1-3, 7-10).

Associated extragenital anomalies, most commonly congenital renal and vertebral anomalies, have been described in several reports (1-3, 8-9, 11-13). Familial occurrence is unusual. Some authors reported cases in which other members of the family showed renal, vertebral or uterus anomalies (2, 8, 12, 14, 15).

The syndrome has been described as a blind-ending introitus vaginae and bicornuate uterine remnants presenting as muscular buds. The fallopian tubes are described as having normal appearances, but may be hypo- or aplastic. The ovaries may show non-descent or may be located in an inguinal hernia. The clitoris, the labia majora and minora are normally developed (1, 2, 6, 8, 9, 11, 16).

II.2 Diagnosis

A simple gynecologic examination will show normal female sex characteristics associated with a blind ending introitus of the vagina. No uterus will be palpable at rectal examination. Additional ultrasound can be helpful to demonstrate the absence of a normally developed uterus and the localization and structure of the ovaries (10, 17-19). Moreover, the kidneys can be studied to diagnose possible associated congenital renal agenesis and/or ectopia (18).

To demonstrate a normal ovarian function the biphasic body temperature patterns should be evaluated. This is also important for the differentiation of the MRKH syndrome from other abnormalities, as will be extensively described in part II.3. In the MRKH syndrome, the endocrine function is supposed to be normal (1-4, 6, 8, 20). However, Egarter et al (21) in a group of 15 patients with the MRKH syndrome and a control group of 4 patients claimed a slight difference between these 2 groups. Further studies need to be done in a representative group of patients.

If no doubt exists about the phenotypical signs, than there is no need to search for chromosomal pathology, since as earlier mentioned, the karyotype in patients with the MRKH syndrome is described to be normal (1-3, 7-10).

Laparoscopy is not necessary for the confirmation of the diagnosis of the MRKH syndrome (10, 13, 19). However, because of some suggestions in the

literature (6, 11) and our idea that the MRKH syndrome associated with serious extragenital anomalies may occur in combination with abnormal fallopian tube development or clear asymmetry in muscular bud development, laparoscopy available of all patients, was retrospectively studied in order to assess the exact state of the internal genitalia. These laparoscopic studies were performed for other reasons, most of them as preoperative studies.

These results will be discussed in chapter VI.

II.3 Differential Diagnosis

To complete this chapter, other anomalies with blind ending vagina and primary amenorrhea with or without cyclic abdominal pain have to be taken into consideration.

Of importance is the androgen insensitivity syndrome (testicular feminisation, male pseudohermaphroditism), which should be differentiated from the MRKH syndrome, since it may resemble a female phenotype with blind-ending vagina. A remarkable sign is that these patients lack axillary and pubic hair (hairless-women). Uterus and fallopian tubes are not developed. The karyotype is 46,XY. The endocrinological situation will be different compared to the MRKH syndrome because the patients have „normal" levels of testosterone and there is no temperature shift caused by ovulation. The testicles are often found in an inguinal hernia (1, 4, 22).

Especially in the prepubertal age, it can be difficult to differentiate this syndrome from the MRKH syndrome, since the lack of sexual hair is not a relevant sign at this age, making confirmation by karyotyping and hormonal investigation more important. However, it is very rare for testicular feminisation, as it is in the MRKH syndrome, to present before puberty, unless a testicle is found in an inguinal hernia (22, 23).

The etiologic factors responsible for the testicular feminisation syndrome are the absence of androgen receptors in the target organs, making these organs unable to bind testosterone, or a 5-alpha-reductase deficiency, important for converting testosterone into dihydro-testosterone, resulting in the inability of the target receptors to recognize the androgens.

Another syndrome which may resemble the MRKH syndrome is the adrenogenital syndrome (female pseudohermaphroditism) resulting from 21-hydroxylase or 11-beta-hydroxylase deficiency in the adrenals, leading to abnormal androgen stimulation disturbing the normal ovarian function. Since a minimal androgen stimulus may prevent the development of the lower vagina, a hypoplastic vagina may be seen in these patients. The karyotype is 46,XX (1, 4). The ovaries and uterus are normal. Phenotypically these patients are females, unless virilization starts before the 20th gestational week. In that case the sexual development may be completely in a male direction. Differentiating this

syndrome from the MRKH syndrome is not difficult, since these patients have a normal uterus, clitoris hypertrophy and hirsutism associated with a high androgen level (1, 24).

An acquired form of the adreno-genital syndrome exists in those patients, where androgen steroids have been given to the mother during pregnancy since androgen steroids can pass the placenta (1, 25) or in patients with an androgen producing tumor of the adrenal or ovary.

The rare cases of true hermaphroditism are seen when ovarian and testicular tissues exist in the same individual. In most cases there is doubt at birth with respect to male or female phenotype. Testicular development is possible only in those situations, where an Y-chromosome exists. The XX/XY mosaicism is found in most patients. An ovo-testis at one side associated with ovary or testis on the other side is seen in many patients (1, 26). The vagina is blind-ending in most cases, but is sometimes normally developed. Nearly always an uterus is present. 75% of the true hermaphrodites are recognized as males (1, 24, 27).

The imperforate hymen is a malformation caused by a transverse septum, occurring after the development of the vaginal plate and simulating vaginal agenesis. The uterus and fallopian tubes are normally developed. These patients will have cyclic abdominal pain because of obstructed menstrual flow, leading to haematometra and haematosalpinx. Inspection of the vulvar area will show a blue coloured protruded hymen. These symptoms and signs make differentiation from the MRKH syndrome easy (4, 8, 10).

The classical Turner syndrome will usually be suspected from a combination of short stature, primary amenorrhea, sexual infantilism, increased distance between the nippels, pectus excavatum, sometimes coarctation of the aorta, elevated levels of gonadotropins and confirmed by the findings of chromosomal abnormalities (XO) (24, 28).

In the MRKH syndrome, the endocrinological hypothalamic-pituitary-ovarian axis is normal (1, 2, 29). The syndrome is therefore easily differentiated from the primary amenorrhea and pubertas tarda caused by disturbances in this axis. The very common idiopatic form of delayed puberty is easily differentiated from the MRKH syndrome since in these patients, as in those with endocrinological disturbances, a normal vagina and uterus are present (23, 30).

To complete this differential diagnostic review, the acquired form in which a functional vagina is absent, has to be mentioned (12, 19). The causes as summarized by Willemsen (1) are:

- inflammation (Difteria, scarlet fever, small pox)
- radiation therapy of the genitalia
- chemical exposure
- traumatic (obstetrical, postsurgical, corpus alienum).

The history and the presence of a normally developed uterus will make it possible to differentiate these patients from those with the MRKH syndrome.

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Chapter III

EMBRYOLOGIC AND ETIOLOGIC ASPECTS

III.1 Introduction

Aplasia of the uterus results from a disorder of the development of the Müllerian ducts occurring between the 4th and 12th gestational week (1-2).

The association between genital and the urinary tract anomalies and abnormalities of the skeletal system has been described repeatedly (1, 3-8).

The genital and the urinary system, develop from the intermediate mesoderm, positioned in between the lateral mesoderm and the medially located paraxial mesoderm. The skeletal system originates from the paraxial mesoderm. These three mesodermal structures result from a subdivision of the middle of the three primary germ layers (ectoderm, mesoderm, entoderm), which is completed at the end of the third gestational week (9-10).

The excretory ducts of the developing urinary- and genital systems initially enter a common cavity, called the cloaca. Between the 4th and 7th gestational week, the cloaca becomes subdivided by the urorectal septum into a ventral part: the urogenital sinus and a dorsal part: the canalis rectalis (9-10).

Because the genitourinary system and the skeletal system originate from the mesodermal mass, because of the spatial relationship and because of partial overlap between the 4th and 6th gestational week (1, 9-11), it seems reasonable to assume that some defect in the organization of the mesoderm could cause the skeletal abnormalities as well as defective mesonephric development with subsequent abnormalities in kidneys and genitalia.

The essence of this chapter is to emphasize the embryology of the anatomical structures involved in the MRKH syndrome and to discuss the etiologic aspects.

III.2 EMBRYOLOGY OF THE UROGENITAL TRACT

III.2.a Wolffian ducts, kidneys

Three subsequent sets of excretory organs develop during embryonic life: the pronephros, the mesonephros and the metanephros (the permanent kidney). By the fourth gestational week the developing urinary tract is represented by the rudimentary pronephros, which is of importance only in that it furnishes the duct of the second system, the mesonephros, and for the rest disappears entirely.

The mesonephros, or Wolffian body, gives origin to the Wolffian duct (9-10). By the end of the 7th gestational week, the Wolffian duct is completed. The metanephros, or permanent kidney, begins to develop early in the 5th gestational week in the metanephric mesoderm, located around the ureteric bud, which is an extension of the Wolffian duct. The ureters eventually arise from these ureteric buds, near the cloaca. Between these ureteric buds and the metanephric mesoderm, developing into the adult kidneys, reciproque induction exists (1, 12). The

permanent kidneys, initially located in the sacral region, migrate cephalad between the 6th and 7th gestational week and attain their adult position by the 9th gestational week (9-10).

III.2.b Müllerian ducts, fallopian tubes, uterus

By the 6th gestational week (around the 37th day) the Müllerian ducts appear in human embryos (1, 5, 9-10). They arise as longitudinal invaginations of the coelomic mesodermal epithelium on the antero-lateral surface of the urogenital ridge (3, 9-10). The cephalic portion develops first and forms the fallopian tubes, the caudal parts of both ducts fuse to form the uterus and probably the proximal part of the vagina (9-10). During the 8th through 12th gestational week, the Müllerian ducts pass caudally, lateral to the Wolffian ducts, but toward the posterior end of the embryo, they cross the medial side of these ducts ending in an epithelial eminence, named the Müllerian tubercle located dorsal to the urogenital sinus (9-10). After contacting the urogenital sinus in the 8th gestational week, paired endodermal outgrowths, called sinovaginal bulbs, are induced to form. These bulbs fuse to form a solid vaginal plate.

According to Wells (13), canalization of the solid Müllerian ducts occurs from the coelomic cavity ostium to the Müllerian tubercle, whereas fusion with the urogenital sinus takes place when canalization of the vagina has finished. Fusion and canalization of the Müllerian ducts have finished in the 16th gestational week (1). In the 4th to the 5th gestational month, the uterus and vagina acquire a single communicating lumen. The hymen appears in the 5th gestational month as a special differentiation of the lower vaginal segment and represents the remains of the urogenital sinus (9-10).

III.2.c Vagina

Because the vaginal plate appears at the junction of the Müllerian ducts, the Wolffian ducts and the urogenital sinus, its origin is still controversial (1, 5). A major uncertainty exists as to the magnitude of the respective contributions of the urogenital sinus and the Müllerian ducts to vaginal development (14-16).

Bulmer (14), in an excellent study of 13 foetuses, concluded that the cellular origin of the vaginal plate is principally from the urogenital sinus, but interaction of both Müllerian duct and urogenital sinus is probably essential for normal vaginal development.

Koff (15) suggested that the fusion of the caudal ends of the Müllerian ducts with the urogenital sinus is followed by a major epithelial proliferation and elongation that results in the formation of an initially solid vaginal plate at about the 30 mm stage. The vagina in turn canalises, beginning at the 150 mm stage. By pressing the urogenital sinus caudalad, the Müllerian tuberculum is formed. The author concluded that at least 2/3 of the vagina is formed from the urogenital sinus. Other embryologists believe that the only urogenital sinus contribution to

the vagina, is the part outside the hymen (17-19) and believe in a major contribution of the Müllerian ducts. The role of the Wolffian ducts in the formation of the human vagina was suggested by Ancien, Drews, Forsberg, Gruenwald, Kempermann, Mijsberg (20-25).

The consensus seems to be that the vagina develops from two structures: the Müllerian duct and the urogenital sinus. The vestibulum unquestionably arises from the urogenital sinus (1, 15). The Wolffian ducts play an important role in the development of the Müllerian ducts (theory of Gruenwald), but a direct role in the formation of the vagina remains questionable.

Of importance is that in the male pseudohermafrodite (testicular feminisation) the testes produce Müllerian Inhibiting Factor (M.I.F.), which suppresses the development of the Müllerian ducts. The usually normal development of the lower third of the vagina in those patients, suggests that at least this part develops from the urogenital sinus (1, 26).

III.2.d Gonads

Although the genetic (chromosomal) sex of an embryo is determined at the time of fertilization, the gonads do not acquire male or female morphological characteristics until the 7th gestational week when testes and ovaries begin to differentiate (9-10, 26). The primitive gonads arise in the fourth gestational week as a pair of longitudinal ridges, the gonadal and genital ridges, and are formed by proliferation of the coelomic epithelium and the underlying mesenchym of parts of the so-called urogenital ridges. The primordial germ cells originate in the wall of the yolk sac and are first identifiable in the third gestational week, migrating by chemotaxis along the dorsal mesentery of the gut to the genital ridges, arriving there in the sixth gestational week (2, 9-10, 21). The differentiation of the primitive gonads into testes, as induced by the primordial germ cells, is largely dependent upon the action of the Y-chromosome, which carries the HY-antigen. This antigen is responsible for the critical induction of the testes, finding its receptor only in the gonads (27-28).

It is only after the testes develop, that the Müllerian ducts regress, the Wolffian ducts differentiate to become ductus deferentes and seminal vesicles, and the auxilliary genital glands and external genitalia are formed. Relevant is the work of Jost (29), who removed the undifferentiated gonadal ridge in rabbit foetuses and showed that females developed with full differentiation of the Müllerian ducts, regression of the Wolffian ducts and complete female cloacal differentiation. This process was termed „basic femaleness" and could only be explained by the presence of a suppressor substance, responsible for the regression of the Müllerian ducts in the male, which is produced by the testes and was called the Müllerian Inhibiting Factor [(M.I.F.) 1, 29]. Production of M.I.F. occurs in the sertoli cell and continues until the age of 2 years (30). Jost (29) also showed, that testosteron implants in the sexually indifferent embryo had no

effect on Müllerian development, but induced development of the Wolffian ducts and virilized the cloaca. Neumann (31) showed that when the developing male is exposed to the antiandrogen cyproteroneacetate, the Wolffian ducts are not evoked, whereas the external genitals are either ambiguous or female. Verschoof (32) reported that ovarian agenesis can be caused by developmental abnormalities in the urogenital ridge followed by anomalies of the Wolffian and Müllerian ducts on the ipsilateral side. However, normal ovaries do not automatically mean a normal development of Wolffian and Müllerian ducts (12, 33).

From these studies it can be concluded that the ovaries do not play an active role in the development of a female phenotype, whereas the testes are of critical importance in the development of a male phenotype by the production of testosteron and M.I.F.

III.3 EMBRYOLOGY OF THE SKELETAL SYSTEM

The skeletal system originates from the paraxial mesoderm which is subdivided into paired segments called somites at the end of the fourth gestational week. These somites form bilateral elevations on the dorsolateral surface of the embryo. Each somite consists of a sclerotome and a dermomyotome. Mesenchymal cells leave the sclerotomes and envelop the notochord, where they give rise to the vertebral column and ribs (9-10). Development of the vertebral column is initiated after the formation of perichordal condensations alternating with loosely packed sclerotomal cells at the end of the fourth gestational week (9-11). Each vertebra develops from the condensation of the caudal half of one sclerotome which fuses with the cranial half of the next sclerotome. By the end of the fourth gestational week, the notochord forms a continuous rod, located centrally in the vertebral column. The notochord eventually disappears as ossifcation of the vertebral column occurs, except for the nucleus pulposus, which forms the centre of each intervertebral disc (9-10).

III.4 MRKH AND ASSOCIATED ANOMALIES

III.4.a Renal

The origin of the Müllerian ducts and their relationship with the Wolffian ducts has been studied in considerable detail by Gruenwald (20). He suggested that the Müllerian system is influenced directly by the development of the Wolffian system because of their close anatomical relatinship. The caudal end of the Müllerian duct becomes so intimately connected with the Wolffian duct, that no basement membrane separates their epithelia. It is only later, after the

solid Müllerian ducts develop a lumen, round the ninth gestational week, that the two become completely separated. Gruenwald concluded that the development of the Müllerian ducts completely depends upon the integrity of the Wolffian ducts and, as a consequence, the Müllerian duct development in caudal direction cannot take place in the absence of Wolffian structures.

The greater incidence of malformation of the genitals in the female, associated with abnormalities of the urinary tract, can now be understood because of the intimate relationship between the two structures (theory of Gruenwald) and because the Müllerian duct arises later in development than the Wolffian duct.

It can be concluded that there are three possibilities:

- arrested development of the Wolffian ducts prior to the sixth gestational week may interrupt the progression of the Müllerian ducts and arrest the formation of the ureter, leading to renal agenesis, with concomittant Müllerian anomalies (1, 12, 22, 32).
- arrested development of the Wolffian ducts between the sixth and ninth gestational weeks, may cause ectopia or malrotation of the kidneys, associated with Müllerian anomalies (1, 21, 34).
- arrested development of the Wolffian duts after the ninth gestational week, may produce malformed genitals only (1, 35).

III.4.b Skeletal

The association with skeletal anomalies is comprehensible because the differentiation of the skeletal system partially overlaps that of the development of the genitourinary tract (1, 9-11). The blastemas of the lower cervical-upper thoracic somites, arm buds, scapulae and pronephric ducts have an intimate spatial relationship at the end of the 4th gestational week (8, 11). It seems reasonable to suggest that an unknown factor, acting in this region during this intimate spatial relationship, at about the end of the 4th gestational week could affect the developing spine (scoliosis, Klippel-Feil), scapulae (Sprengel deformity), uropoetic tract (renal agenesis/ectopia) and upper extremities (arm agenesis, first ray agenesis/hypoplasia). All these associated anomalies have been mentioned previously (1, 3-8) and Duncan (36) introduced the term: MURCS-association (Mu = Müllerian duct aplasia/hypoplasia; R = renal agenesis/ectopia; CS = cervical somite dysplasia). In his report he mentioned also Sprengel deformity and upper extremity pathology.

III.5 ETIOLOGIC ASPECTS

The etiology of the MRKH syndrome is still a matter of dispute in the literature. There are some reports (3, 37-39) dealing with rare cases of familial occurrence of the syndrome, suggesting an inherited autosomal recessive

disorder. There are other publications (8, 40) of cases of monozygotic twins, where only one twin was affected by the syndrome. According to Litschke (40) it is possible that the disconcordance of the vaginal agenesis in identical twins results from variable manifestations of an underlying defect, rather than a nongenetic cause for the abnormality. Griffin (3) describes a family in which one patient did have the MRKH syndrome associated with congenital agenesis of one kidney and severe scoliosis, whereas a sister had scoliosis without the signs of the MRKH syndrome and a maternal aunt had a double uterus. He suggested these three cases to be the result of a variable expression of one gen. Both the multiplicity of associated anomalies and the high frequency of some of those support the etiologic concept of variable expressions of a genetic defect, possibly precipitated by teratogenic exposure (3, 5). If congenital absence of the vagina can represent only one manifestation of a variably expressed genetic defect, ascertainment may not be adequate in most instances, so that the real frequency of familial involvement has been underestimated. When more families of patients with the MRKH syndrome are systematically analysed for instances of isolated skeletal and renal abnormalities, spontaneous abortion, that might result from congenital absence of both kidneys (41), and involvement of the analogous syndrome in male relatives [congenital absence of vas deferens, which is also associated with a high frequency of anomalies of the urinary tract (3)], the results may support the idea of a variably expressed genetic defect.

With regard to the teratogenic hypothesis, Evans (5) and others (8, 42) have implicated this possibility because of the fact that the MRKH syndrome may occur after embryogenic exposure (round the 37th to the 41th gestational day), to known teratogens such as thalidomide (43).

Another hypothesis proposed by Schmid-Tannwald and Hauser (44) may also be of significance. As stated earlier, in the male regression of the Müllerian ducts is a physiological event, occurring under the action of the Müllerian Inhibiting Factor (M.I.F.), produced in the medullary part of the undifferentiated gonad. Like other authors (5, 8, 21, 42) Hauser believes that a limited medullary gonadal differentiation with consequent M.I.F. production leads to a defective development of the Müllerian ducts, since the gonadal differentiation and regression of the Müllerian ducts occur at the same time. Depending on the time of beginning of M.I.F. production, the development of the Müllerian ducts would stop at various stages.

The data presented in chapter IV-VIII show a fairly high prevalence of associated malformations in the MRKH syndrome. However, all these associated malformations also occur as separate features. A multifactorial genesis has to be considered when one sole cause can not be proven (45).

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Chapter IV

EVALUATION OF RADIOGRAPHIC ABNORMALITIES OF THE HAND IN PATIENTS WITH THE MAYER-ROKITANSKY-KÜSTER-HAUSER SYNDROME

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IV.1 ABSTRACT

Radiographs of the hand in a group of 40 patients with the Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome were studied. Most of the patients had the following abnormalities: brachymesophalangy of digits 2-5 (22/39 patients), small distal phalanx of digit 1 (22/39 patients), long proximal phalanx of digits 3-4 (19/39 patients), and long metacarpals of digits 1-4 (20/39 patients). In addition, three patients had distinct radial dysplasia and abnormalities of the carpals.

IV.2 INTRODUCTION

The Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is primarily the congenital absence of the uterus and vagina. Associated anomalies of the renal system (pelvic kidney or one absent kidney) are found in 36% of cases (3-5, 8, 10-12). The association of congenital deafness and facial abnormalities is very rare (12). Abnormalities of the skeletal system are found in 10% of cases (10-12). Abnormalities of the vertebrae (wedge-shaped vertebrae, fusion of vertebrae, Klippel-Feil syndrome) and abnormalities of the extremities (phocomelia, radial hypoplasia) have been described previously. In particular, the combination of the MRKH syndrome and the Klippel-Feil syndrome has been mentioned repeatedly (1, 4, 6, 8, 10, 11). Superficial descriptions have been made of radiographic abnormalities of the hand in MRKH syndrome (2-4, 8, 10); however, to our knowledge such abnormalities have never been studied systematically. The present study was occasioned by finding serious abnormalities in the skeleton of the hand in two patients with the MRKH syndrome. These abnormalities consisted of radial hypoplasia; a long and slender first metacarpal; hypoplasia of the scaphoid, and an abnormally formed, distally positioned trapezium (Fig. 1A). Such abnormalities are present also in the Holt-Oram syndrome (association of radial dysplasia and cardiac pathology, especially atrium septum defect) (7, 9). In one of the two patients we found evidence for both the Holt-Oram syndrome and the MRKH syndrome (Fig. 1B). In order to evaluate the abnormalities of the hand in patients with the MRKH syndrome, we studied the radiographs of the hand in 40 patients.

IV.3 MATERIAL AND METHODS

Radiographs of the hand of 40 patients were studied. These patients had been referred to the department of radiology of the University Hospital Groningen (15 patients) and the St. Radboud Hospital, University of Nijmegen (25 patients). The radiographic study of one patient was incomplete. In the scrutiny of the

radiographs special attention was paid to: (1) metacarpal index [7], (2) metacarpal sign [7], (3) carpal angle [7], (4) pattern profile analysis [7], (5) other findings.

The metacarpal index is the average of the relative slenderness values of the second to the fifth metacarpal $\frac{rs2+rs3+rs4+rs5}{4} = mci$).

The relative slenderness is defined as the quotient of the maximum length and the width, measured exactly halfway these metacarpals.

The metacarpal sign is defined by drawing a line tangentially to the head of the fourth and fifth metacarpals. Normally this line does not touch the head of the third metacarpal. The carpal angle is the angle between the line tangential to the scaphoid and lunate and the line tangential to the lunate and triquetrum.

In order to define the pattern profile analysis the maximum length of all metacarpals and phalanges must be measured. The resulting lengths are compared with the normal values as described in the tables of Garn (7, 9). In this way is determined the degree to which the derived values differ from the normal. These differences are represented by numbers that indicate the quotient of the measured deviation and the standard deviation. These quotients are represented graphically, and this results in the pattern profile analysis (7). We determined a mean pattern profile analysis by calculating the mean values of the length of all the metacarpals and phalanges.

The heading other findings represents the nonmeasureable abnormalities.

IV.4 RESULTS

1. Metacarpal index. The values of the metacarpal index in our group of patients ranged from 6.1 to 9.0 (normal values: 6.5-7.9) [7]. In 17 cases the measured value was within the normal range; in 11 cases the metacarpal index exceeded 7.9; in one case it was less than 6.5; and in five cases it was 7.9 (table 1). Unfortunately the metacarpal index of one patient could not be determined.

2. Metacarpal sign. In six cases the metacarpal sign was abnormal (table 1).

3. Carpal angle. The values of the carpal angle vary from 105-141 degree. The 5th to 95th percentile range lies between 115.0°-146.5° [7]. In our group of patients the value of the carpal angle was less than 115° in six cases. In none of the cases did the value exceed 146.5° (table 1).

4. Pattern profile analysis. A graph contour representative of the MRKH syndrome could not be established. Three types of graph could be distinguished: (1) graphs which lay completely below the normal line (13cases) (Fig. 2B); (2) graphs which lay completely above the normal line (13 cases) (Fig. 3B); (3)

graphs which were both above and below the normal line (13 cases) (Fig. 4) (table 1).
Comparison of the corresponding values of the patients showed brachymesophalangy of digits 2-5 in 22 out of 39 hands, longer proximal phalanges of digits 3-4 in 19 out of 39 hands, longer metacarpals 1-4 in 20 out of 39 hands, and a small distal phalanx of digit 1 was found in 22 out of 39 hands. In comparison with the mean pattern profile analysis the results were the same (Fig. 5). In one case a complete graph could not be obtained.

5. Other findings. Other findings consisted of: radial hypoplasia (three patients), hypoplastic and abnormally formed scaphoid (three patients), distally positioned and hypoplastic trapezium (three patients), clinodactyly of digit 5 (two patients), pointed distal phalanx of digit 1 (one patient), and coarse trabecular pattern (one patient) (table 1).

IV.5 DISCUSSION

According to the literature, congenital abnormalities of the skeleton are found in about 10% of the patients with the MRKH syndrome (10-12). The simultaneous occurrence of genital anomalies, urinary tract anomalies, and skeletal malformations is understandable, since all the three structures originate from the mesoderm in the same embryological period.

Our results show that a number of abnormalities of the hand are found in patients with the MRKH syndrome. Some abnormalities can only be recognized by measurement (carpal angle, metacarpal index, brachymesophalangy), others can be diagnosed visually (clinodactyly, radial hypoplasia, scaphoid hypoplasia, too distally positioned and abnormally formed trapezium).

In our group, three patients showed serious abnormalities of the hand. These three patients presented the following findings: radial hypoplasia, scaphoid hypoplasia, hypoplasia and too distally positioned trapezium, abnormal first digit (Fig. 1A). These abnormalities are not characteristic of the MRKH syndrome and have also been seen in the Holt-Oram syndrome (7, 9). One of the three patients showed features of the MRKH syndrome as well as the Holt-Oram syndrome (Fig. 1B).

The combination with the Klippel-Feil syndrome and other congenital abnormalities such as the Holt-Oram syndrome, abnormalities of the urogenital tract, and other skeletal abnormalities have been extensively described by Ramsey and many other (1, 4, 6, 8, 10-12). Of our three patients with serious abnormalities of the hand, one patient also suffered from the Klippel-Feil syndrome. In the overall group of 40 patients there were three patients with the Klippel-Feil syndrome. The co-existence of the MRKH syndrome and the Klippel-Feil syndrome is rare (10-11).

Apart from the three patients with serious abnormalities of the hand, most other patients also had less severe abnormalities. Relatively often (11/39 cases) the metacarpal index exceeded the normal range value of 7.9. The metacarpal sign was positive in 6 out of 39 cases; these patients had a relatively short fourth metacarpal. The carpal angle was lower than the fifth percentile at 115° in 6 out of 39 patients; this is not specific and has been described in other disorders (7, 9). The evaluation of the pattern profile analysis shows that corresponding abnormalities appeared to occur in many patients: (1) longer metacarpals 1-4 (20/39); (2) longer proximal phalanges of digits 3-4 (19/39); (3) brachymesophalangy of digits 2-5 (22/39); (4) small distal phalanx of digit 1 (22/39). The following combinations were seen: (a) combination 1 and 2 (13/39); (b) combination 3 and 4 (17/39). This shows that longer metacarpals 1-4 and longer proximal phalanges of digits 3-4 are found frequently as is the combination of brachymesophalangy of digits 2-5 and a small distal phalanx of digit 1. This is shown graphically in the curve of the mean pattern profile analysis (Fig. 5).

Although the abnormalities are not characteristic for the MRKH syndrome and have been described in other disorders (7, 9), the combinations of abnormalities which we found in evaluating the pattern profile analysis may be of significance.

In a group of 40 patients with the MRKH syndrome a wide range of abnormal radiographic findings of the hand were found, varying from serious carpal and radial dysplasia (3/39) to less severe abnormalities that can only be measured. Although the abnormalities are not characteristic in themselves and have been described in other disorders, it appears that with the MRKH syndrome more or less characteristic combinations of abnormalities of the hand skeleton can be found. It can be concluded that in patients with the MRKH syndrome it is necessary not only to seek abnormalities of the urinary tract but also to study the skeletal system (vertebrae, hands).

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Table 1

Patient	C.A.	M.C.S	M.C.I	P.P.A	R.F.
1	123	abn	8.0+	→	None
2	108[a]	N	9.0+	→	Radial hypoplasia; trapezium to distal + hypoplasia; scaphoid hypoplasia
3	134	N	7.4	↓	None
4	105[a]	N	7.9-	→	Coarse trabecular pattern
5	124	N	6.8	↓	None
6	134	N	7.1	↓	None
7	141	N	7.9-	→	None
8	132	abn	8.5+	↓	None
9	113	N	7.9-	→	None
10	111[a]	N	7.8	↑	Clinodactyly 5th digit
11	123	N	7.0	↑	None
12	115	N	7.1	→	None
13	128	N	6.6	↓	None
14	118	N	8.2+	↑	Radial hypoplasia; scaphoid hypoplasia; pointed, slender distal phalanx thumb; trapezium too distal + hypoplasia
15	120	N	7.2	↑	None
16	119	N	7.3	↑	None
17	135	abn	8.7+	↓	None
18	128	N	7.5	→	None
19	135	N	7.9-	↓	None
20	119	N	7.5	→	None
21	133	N	7.2	incomplete	None
22	130	N	7.2	→	None
23	128	abn	7.9-	↑	None
24	118	N	7.3	↓	None
25	111[a]	abn	6.10	↓	Clinodactyly 5th digit
26	138	N	8.2+	↑	None
27	115	N	8.0+	↑	None
28	118	N	7.1	↓	None
29	140	N	6.8	↑	None
30	132	N	7.6	↑	None
31	137	N	8.2+	↑	None
32	130	N	6.8	↓	None
33	121	N	7.8	→	None
34	114[a]	N	8.4+	→	None
35	128	N	not to define	↑	None
36	130	N	8.9+	→	None
37	126	abn	7.7	↑	None
38	123	N	8.0+	→	None
39	111[a]	N	7.2	↓	None
40	127	N	7.5	↓	Radial hypoplasia; scaphoid hypoplasia; trapezium too distal + hypoplasia; pointed slender distal phalanx thumb

Abbreviations used in table 1:
C.A. = Carpal angle ([a] too small)
M.C.S. = Metacarpal sign (N = normal, abn = abnormal)
M.C.I. = Metacarpal index (+ = above normal, 0 = below normal, - = margin)
P.P.A. = Pattern profile analysis (↑ = above N, ↓ = under N, → = above + under N)
R.F. = Rest findings

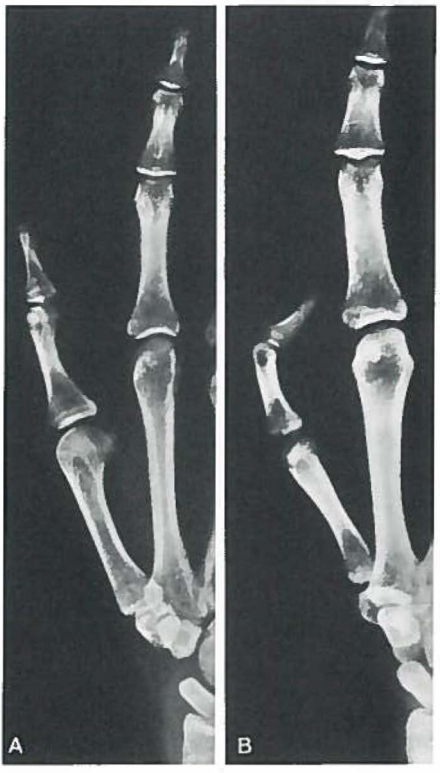

Fig. 1.A
Radiograph of the hand of a patient with the MRKH syndrome

Fig. 1.B
Radiograph of the hand of a patient with MRKH syndrome in combination with the Holt-Oram syndrome. Hypoplasia and abnormally placed carpals at radial side of the hand; slender first meacarpals. No distinction between abnormalities A and B.

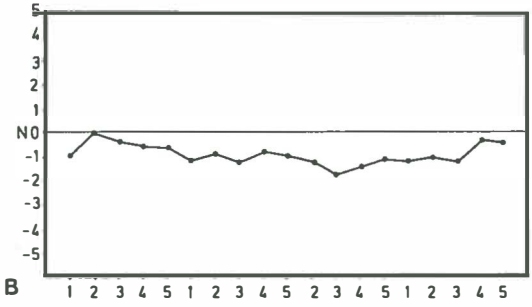

Fig. 2.A
Radiograph of the hand of a patient with the MRKH syndrome "normal findings". When measured, however, most phalanges appeared to be too small.

Fig. 2.B
Pattern profile analysis of the hand from the patient of A.

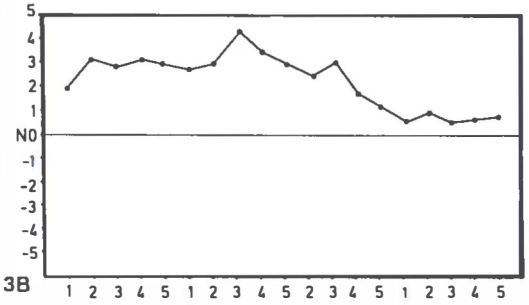

Fig. 3.A
Radiograph of the hand of a patient with the MRKH syndrome "normal findings". When measured, however, most phalanges appeared to be too long

Fig. 3.B
Pattern profile analysis of the hand from the patient of A

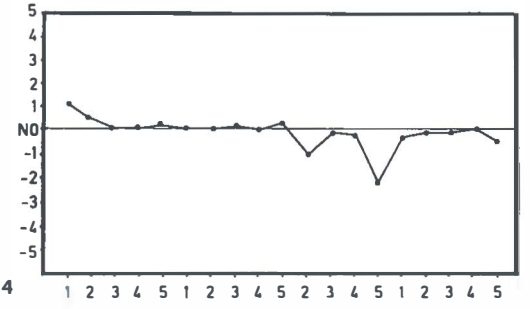

Fig. 4.
Pattern profile analysis of a patient with the MRKH syndrome. Example of a graph above and below the normal line.

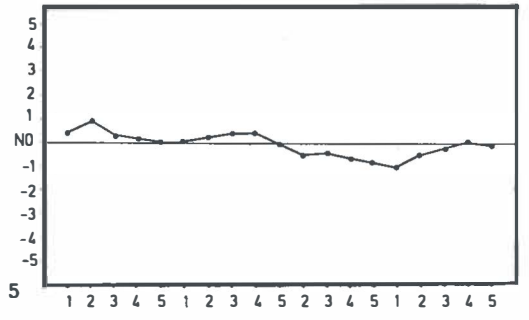

Fig. 5.
Mean pattern profile analysis

Chapter V

SPINAL ABNORMALITIES AND THE ATYPICAL FORM OF THE MAYER-ROKITANSKY-KÜSTER-HAUSER SYNDROME

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V.1 ABSTRACT

In 96 patients with congenital absence of the uterus and upper vagina, the Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, it proved possible to distinguish between the typical and the atypical form using laparoscopy.

The typical form was characterized by symmetrical nonfunctioning muscular buds (the Müllerian ducts remnants) and normal fallopian tubes, and the atypical form by aplasia of one or both buds, one bud smaller than the contralateral one, with or without dysplasia of one or both fallopian tubes.

The atypical form was found in 52 patients (54.2%).

Radiographs of the spine showed congenital spinal abnormalities in 37 patients. Especially the Klippel-Feil (KF) syndrome was seen in 14 of 52 patients with the atypical form only. Renal agenesis or ectopia together with the MRKH- and KF syndromes known as the MURCS association (MU = Müllerian duct aplasia; R = Renal agenesis/ectopia; CS = Cervical somite dysplasia), was diagnosed in 11/52 patients in the atypical group.

From our results we conclude that additional cervical spine films in patients with the MRKH syndrome are indicated only in the atypical form of the syndrome. In those cases where the MRKH syndrome is associated with the KF syndrome, the MURCS association should be considered.

V.2 INTRODUCTION

Congenital absence of the uterus and vagina, the Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, is a fairly rare disorder. The incidence has been variously reported as 1 in 4000-5000 female births (3, 18, 30).

Patients with the MRKH syndrome have a 46,XX karyotype and normal secondary sex characteristics. The external genitalia are normal in appearance, but only a shallow vaginal pouch is present. The ovarian function is normal (12, 22, 30).

Although there is no normal uterus, bilateral nonfunctioning rudimentary uterine anlagen in the form of symmetrical small non-canalized muscular (myometrical) buds (Müllerian ducts remnants) are present (4, 14, 22, 30, 32).

In 6-10% of cases endometrial tissue or even a variable uterine development with hematometra may be present, resulting in cyclic abdominal pain (2, 16, 30, 32).

In 1977 Schmid-Tannwald and Hauser described differences of the internal genitalia with respect to the classic form in 10 patients, on the base of laparotomy (21). These differences were: asymmetrical uterine remnants (aplasia of one or both muscular buds, and when both muscular buds were found, one was larger than the other) and abnormalities of the fallopian tubes (hypoplasia/aplasia of one or both tubes).

In 1982 this difference was also emphasized in 6 patients by Ghirardini et al. (9), and in 1988 it was recorded by Heidenreich (14) in 15 patients with associated extragenital anomalies that asymmetry in the muscular buds and/or abnormally developed fallopian tubes was present.

Associated congenital abnormalities of the skeletal system have been described to occur in 10-20% of cases (26, 29, 30, 31). The observation that some patients in the atypical group had congenital cervical spine anomalies initiated this study. Congenital fusion (failure of segmentation) of cervical vertebrae is known as the Klippel-Feil (KF) syndrome. The KF syndrome occurs approximately once in 30.000 to 40.000 living births (both male and female) (5, 10, 11, 25, 31). Combination of the KF syndrome with hearing loss has been described (14, 18, 25) and a higher susceptibility to spontaneous fractures in the cervical spine has been suggested (23). When the MRKH syndrome is combined with the KF syndrome and renal agenesis or ectopia the condition is known as the MURCS association (MU = Müllerian duct aplasia; R = renal agenesis/ectopia; CS = cervical somite dysplasia) (6, 7, 9, 14, 15, 33). In order to assess the prevalence of these syndromes in our patientgroup and their combination, we performed routine radiography of the spine in all patients and reviewed the intravenous urography films in those patients who proved to have the KF syndrome. Cooperation with the Department of Obstetrics and Gynecology provided, a comparatively large group of patients with the MRKH syndrome.

V.3 MATERIAL AND METHODS

In a 10-year period (1980-1990) the Department of Obstetrics and Gynecology of the University Hospital, Nijmegen, was attended by 96 patients with the MRKH syndrome. Eigthy of these 96 patients presented with primary amenorrhea, 10 with complaints of dyspareunia and 6 with infertility. In 9 patients, associated cyclic abdominal pain was reported, explained by a hemiuterus with hematometra in 4 patients and by small elements of endometrial tissue in one of the muscular buds in 5 patients. The patients, ranging in age from 15 to 45 years (mean 24.6 years), all had normal female characteristics. Thirty-five patients who were screened proved to have normal female karyotypes. The laparoscopic findings of all patients were reviewed in order to establish which form of the syndrome was present in each - the typical or the atypical form.

In 90 patients, routine anteroposterior and lateral radiographs of the cervical, thoracic and lumbar spines were studied. For 6 patients only the medical reports were available. In those patients with associated congenital anomalies of the cervical spine, previous intravenous urograms were reviewed in order to decide the relationship of the MURCS association. The results of this review will be presented in a separate study (27).

V.4 RESULTS

At laparoscopy the typical form of the MRKH syndrome was found in 44 patients (45.8%), the atypical form in 52 patients (54.2%). The findings of associated spinal anomalies are presented in table 1. Common spinal anomalies such as spina bifida occulta and sacralization of the fifth lumbar vertebra were found in 5/44 (11.4%) patients of the typical group.

The common anomalies in a considarable higher frequency and all severe anomalies were seen in 37/52 (71%) patients with the atypical form of the MRKH syndrome. Of these, 14 were found to have fusion of cervical vertebrae at one or more levels, interpreted as the KF syndrome. Dividing the KF syndrome into subtypes, as suggested in the literature, subtype 1, with massive fusion of cervical and upper thoracic vertebrae in combination with the classical triad of short neck, low hairline, and limited cervical movements, was found in 5 patients (Fig. 1), and subtype 2, with fusion of vertebrae at only one or two cervical levels, was found in 6 patients, while subtype 3, the combination of subtype 1 with massive lumbar fusion, was seen in 3 patients (Fig. 2) (1, 3, 5, 19, 23). Of these 14 KF patients, 11 proved to have congenital renal abnormalities (renal agenesis in 7 cases and pelvic kidney in 4 cases) at intravenous urography, confirming the MURCS association.

V.5 DISCUSSION

The Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is a disorder of the development of the Müllerian ducts occurring between the 4th and 12th week of gestation (4, 12, 14, 18, 30). The syndrome is described as associated with congenital spinal anomalies (26, 29, 30-32). In the single previously reported large series of patients, a 10% prevalence of spinal abnormalities was found in patients with vaginal aplasia (29).

The association between fusion of cervical vertebrae and the MRKH syndrome is considered to be unusual (1, 7, 31). However, we found a 14.6% occurrence (14/96) of this combination, which is higher than the 6-10% stated in the literature, probably due to a more uniform selection and a larger number of patients.

The fact that there is an intimate relationship between the upper part of the spinal somites, the upper extremities, and the pronephros at the end of the 4th gestational week, may explain the occurrence of malformations of these structures in combination with the MRKH syndrome (6, 7).

Abnormalities of the upper extremities associated with the MRKH syndrome have been described elsewhere (26).

The association of the MRKH syndrome and congenital anomalies of the cervical spine in combination with congenital renal anomalies was first described

by Duncan and co-workers in 1979 (7). They called it the MURCS association. We found this association in 11 out of 14 patients.

Whether there is a relationship between sacral agenesis and the atypical form of the MRKH syndrome, as found in 2 patients, remains subject for further studies as it is not previously mentioned in the literature. Sacralization of the fifth lumbar vertebra in patients with the atypical form of the syndrome is not believed to be related to the MRKH syndrome. The prevalence of spina bifida occulta in the typical group is only slightly higher than in the normal population, and may be a chance finding (24). Scoliosis as seen in subtypes 1 and 3 of the KF syndrome of our patient group is common in massive congenital fusion of vertebrae, as normal spinal development is not possible where there are multiple fusions of spinous processes, laminae, and vertebral bodies (1, 10, 11, 19). This was present in 10 patients of which 8 proved to have the KF syndrome.

The differentiation between the typical and the atypical form of the MRKH syndrome is relevant as there was a high coincidence of skeletal and renal anomalies in the atypical form only. In our study the differentiation was made by means of laparoscopy. It has been suggested that laparoscopy could be replaced by MRI or ultrasonography (8, 17, 20). It remains questionable wether MRI can differentiate as accurately as laparoscopy, although the recent study of Fidele and co-workers (8) might provide a starting point. In small series of patients MRI has been described as useful in establishing the presence of small elements of endometrial tissue in those cases where cyclic abdominal pain exists (2, 8, 28). The state of the art in ultrasonography has reached a point where in many situations we may ascertain what we want to know about the uterine, adnexal, and renal status (17, 20). However, reliable distinction between aplasia of one muscular bud, one bud smaller than the contralateral one, and/or aplasia/hypoplasia of one or both fallopian tubes, which are the main features of the atypical form of the MRKH syndrome, needs to be assessed in representative patient groups, as in the literature no reports could be found about reliable discrimination between muscular bud asymmetry and/or fallopian tube dysplasia by ultrasound only. Renal ultrasound, however, is to be prefered to intravenous urography. In our patients we reviewed the previously gathered information on intravenous urography, in order to keep the data as uniform as possible.

The MRKH syndrome is divided into a typical and an atypical form. In this study a higher incidence of the KF syndrome was found than in the literature; all KF syndrome patients had the atypical form. Association between KF anomalies and congenital renal abnormalities (MURCS) was found in the atypical form only. We therefore conclude that in patients with cervical spine anomalies and features of MRKH further investigations (preferably with ultrasound) of the kidneys are indicated.

Future studies are required before it can be stated whether MRI can differentiate accurately between the typical and the atypical form of the MRKH syndrome.

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Table 1. Spinal anomalies as radiographic finding in 96 patients with Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome

Anomalies	Numbers of features			
	Patients with atypical MRKH (N - 52)		Patients with typical MRKH (N - 44)	
	n	%	n	%
KF syndrome	14	26.9	-	
subtype 1	5	9.6	-	
subtype 2	6	11.5	-	
subtype 3	3	5.8	-	
Scoliosis	10	19.2	-	
Sacral agenesis	2	3.9	-	
Sacralization L5	5	9.6	1	2.3
Spina bifida occulta	25	48.1	4	9.1
Fusion L2-3	1	1.9	-	
No. of patients	37	71.2[a]	5	11.4

[a] Fifty-seven features were found in 37 patients. Scoliosis combined with Klippel-Feil (KF) syndrome was found in 8 patients, while spina bifida occulta in combination with KF syndrome was seen in 12 patients.

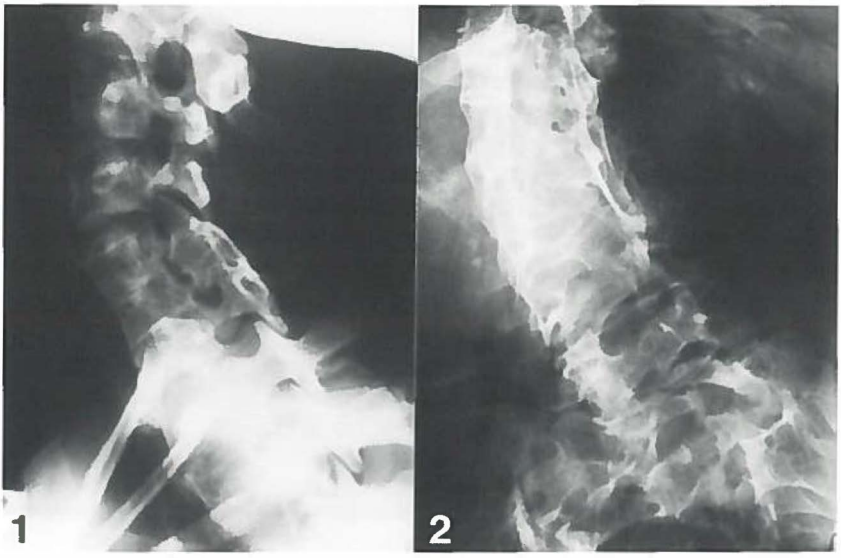

Fig. 1. The Klippel-Feil syndrome subtype 1. Fusion of lower cervical and upper thoracic vertebrae into bony blocks. This patient proved to have the atypical form of the Mayer-Rokitansky-Küster-Hauser syndrome

Fig. 2. The Klippel-Feil syndrome subtype 3. Massive fusion of cervical, thoracic, and lumbar vertebrae (only the lumbar spine is shown here). The patient proved to have the atypical form of the Mayer-Rokitansky-Küster-Hauser syndrome and the MURCS features (Müllerian duct aplasia, renal agenesis ectopia, cervical somite dysplasia)

Chapter VI

MAYER-ROKITANSKY-KÜSTER-HAUSER SYNDROME: DISTINCTION BETWEEN TWO FORMS BASED ON EXCRETORY UROGRAPHIC, SONOGRAPHIC, AND LAPAROSCOPIC FINDINGS

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VI.1 ABSTRACT

OBJECTIVE. The purpose of this study was to discriminate typical (type A) from atypical (type B) Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome (congenital absence of vagina and uterus) and determine their association with renal anomalies and ovarian disease.

MATERIALS AND METHODS. The excretory urographic, sonographic, and laparoscopic findings in 91 patients with MRKH syndrome were compared retrospectively. Symmetric muscular buds and fallopian tubes were diagnostic of type A, and asymmetric muscular buds or abnormally developed fallopian tubes were diagnostic of type B.

RESULTS. On the basis of laparoscopic findings, type A was diagnosed in 40 patients (44%) and type B was diagnosed in 51 patients (56%). Renal anomalies were found in 34 (37%) of the 91 patients, all of whom had type B syndrome. Renal agenesis and a pelvic kidney were the most common findings in the upper part of the urinary tract. Ovarian abnormalities were seen in 14 patients (15%), all of whom had type B syndrome. Sonography did not allow discrimination between types A and B in patients with normal kidneys (17/51=33%), but it provided important information in patients with associated cyclic abdominal pain, in cases of diagnostic dilemma, and in patients with associated renal anomalies.

CONCLUSION. Discrimination between type A and type B of MRKH syndrome is important because associated renal and ovarian abnormalities occur only in type B. Laparoscopy is still needed to discriminate between these two forms. Sonography is useful for diagnosing cyclic abdominal pain and associated renal anomalies.

VI.2 INTRODUCTION

Congenital absence of the uterus and vagina, the Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, is a rare disorder. The prevalence has been reported as one in 4000-5000 female births (1-5).

Patients with MRKH syndrome have a 46,XX karyotype and normal secondary sex characteristics. The external genitalia appear normal, but only a shallow vaginal pouch is present. Ovarian function is normal (4-6).

The typical form of the syndrome is characterized by the absence of both the vagina and the uterus. Only symmetric uterine remnants (the muscular buds), normal fallopian tubes, and normal ovaries are present (1, 4, 5, 7-10) (Fig. 1).

In 1977, on the basis of laparoscopic findings in 10 patients, Schmid-Tannwald and Hauser (8) described abnormalities of the internal genitalia that differed from the typical form of MRKH syndrome. These differences included asymmetric uterine remnants (aplasia of one or both muscular buds, and when

both muscular buds were found, one muscular bud was larger than the contralateral one) and abnormalities of the fallopian tubes (hypoplasia or aplasia of one or both tubes). In seven of these 10 patients, congenital renal abnormalities were seen. They also noticed ovarian disease in 10 patients: cystic ovaries, or anomalies in form or position of the ovaries. They called their findings the atypical form of MRKH syndrome.

We retrospectively reviewed the sonographic, excretory urographic, and laparoscopic findings in 91 patients with MRKH syndrome to determine imaging features that can be used to distinguish typical from atypical forms and to correlate the association of congenital renal anomalies with these two entities.

VI.3 MATERIAL AND METHODS

From 1982 to 1990 at the University Hospital Nijmegen in the Netherlands, MRKH syndrome was diagnosed in 91 patients between 15 and 45 years old (mean age, 25 years). The diagnosis was based on findings at physical examination and laparoscopy in all patients. Signs and symptoms included primary amenorrhea (78%), sterility (9%), and dyspareunia (13%). None of the patients had a medical history that suggested urologic disease (pain, hypertension, pyelonephritis, urinary abnormalities) or testicular feminization. In retrospect, no indication of MRKH syndrome could be found in the relatives of these women. Nine patients (10%) also complained of concomitant cyclic abdominal pain. On the basis of laparoscopic findings, a distinction was made between typical (type A) and atypical (type B) forms: patients with type A had symmetric muscular buds and normal fallopian tubes (Fig. 1); patients with type B had asymmetric muscular buds (aplasia of one or both buds or, when both buds were found, one bud smaller than the other one), or abnormally developed fallopian tubes (hypoplasia or aplasia of one or both tubes) (Fig. 2).

In all patients, excretory urograms were obtained in order to exclude congenital urinary tract abnormalities. Sonography was performed in 25 patients because of cyclic abdominal pain (nine) or because of difficulty in diagnosis. All abdominal and pelvic sonograms were obtained with standard real-time equipment (3.5-Mhz sector scanner) and analyzed for the presence of uterine and renal abnormalities.

We retrospectively reviewed the excretory urograms, sonograms, and laparoscopic findings. Renal agenesis was diagnosed on the basis of findings on excretory urograms, that is, no opacification of the urinary tract on one side, a normal or enlarged kidney on the other side, and no other abnormalities. Renal hypoplasia was diagnosed if the kidney was very small but otherwise similar to a normal organ (11).

VI.4 RESULTS

On the basis of laparoscopic findings, type A MRKH syndrome was diagnosed in 40 patients (44%) and type B was diagnosed in 51 patients (56%). The abnormal laparoscopic findings included aplasia of one muscular bud (11 cases), aplasia of both muscular buds (four cases), one muscular bud smaller than the other (seven cases), aplasia or hypoplasia of one fallopian tube (eight cases), aplasia or hypoplasia of both fallopian tubes (seven cases), fallopian tube aplasia or hypoplasia and muscular bud aplasia (10 cases), and unicornuate uterus with hematometra (four cases).

Laparoscopy showed additional abnormalities of the ovaries in 14 patients (15%), all of whom had type B syndrome. These findings included inguinal hernia containing an ovary (six cases), no descent of ovary (five cases), agenesis of one ovary (one case), and streak ovaries (two cases).

Anomalies of the upper urinary tract were seen on excretory urograms in 34 patients (37%), all of whom had type B MRKH syndrome (34/51=67%). The renal abnormalities included renal agenesis (17 cases), pelvic kidney (eight cases), renal agenesis and contralateral pelvic kidney (five cases), renal hypoplasia (three cases), and horseshoe kidney (one case).

In 21 of 25 patients (five type A; 20 type B) examined with sonography, agenesis of the uterus was confirmed. In four patients with cyclic abdominal pain, a unicornuate uterus with hematometra was found. In five other patients with cyclic abdominal pain and type B syndrome, symptoms were attributed to the laparoscopic finding of a small amount of endometrial tissue inside the bud(s); the pain resolved after the tissue was surgically removed. This abnormality was not detected on sonograms in any case. In all 25 patients, sonography confirmed the results of excretory urography. Eight of these patients had renal agenesis, a pelvic kidney, or both.

We compared congenital anomalies of the urinary tract with laparoscopic findings of the internal genitalia, with respect to the side on which they occurred. Unilateral anomalies of the urinary tract were found to be associated with ipsilateral uterine bud agenesis or fallopian tube dysplasia (16 cases), contralateral uterine bud agenesis or fallopian tube dysplasia (three cases), or bilateral uterine bud agenesis or fallopian tube dysplasia (nine cases). Bilateral anomalies of the urinary tract were found to be associated with unilateral uterine bud agenesis or fallopian tube dysplasia (two cases) and bilateral uterine bud agenesis or fallopian tube dysplasia (four cases).

These results show that three of the 19 patients with unilateral urinary tract anomalies had uterine bud agenesis or fallopian tube dysplasia on the other side.

VI.5 DISCUSSION

MRKH syndrome is defined by the congenital absence of the vagina and the uterus. Instead of a normal uterus, patients with MRKH syndrome have bilateral nonfunctioning rudimentary uterine anlagen in the form of small, noncanalized, muscular (myometrial) buds (Müllerian duct remnants) (1-6). In 6-10% of cases, however, endometrial tissue or even variable development of the uterus with hematometra may be present, resulting in cyclic abdominal pain (4, 7, 12-14). Associated congenital anomalies of the upper urinary tract are reported to occur in 30-40% of all cases, and the most common are renal agenesis and pelvic kidney (2-7, 15).

Both typical and atypical forms of this disease have been described. In 1982, this distinction was noted by Ghirardini and Segre (9) in six patients. In 1988, Heidenreich (10) found a combination of congenital renal anomalies next to asymmetric buds or abnormally developed fallopian tubes in 15 of 51 patients with MRKH syndrome. However, he did not define his findings in a typical or atypical form. In the present series of 91 patients, more than half (51) of the patients with the clinical MRKH syndrome had the atypical form. We therefore suggest that the typical and atypical forms of the disease be designated „type A" and „type B", respectively. Various frequencies have been reported for anomalies of the urinary tract, especially agenesis or ectopia of kidneys, in the general population. Fore et al. (16), using autopsy reports, reported a frequency of one in 920 to one in 1850 (0.1-0.05%), which is in agreement with other reports summarized by Felding (17).

In our group of 91 patients with MRKH syndrome, 34 (37%) had associated congenital anomalies of the urinary tract, and all had type B syndrome (34/51=67%), which confirms the results of Schmid-Tannwald and Hauser (8). No specific data are known on what percentage of women with an absent kidney might have MRKH syndrome. In 40-50% of patients with renal agenesis, an associated genital anomaly has also been found (17, 18).

Schmid-Tannwald and Hauser (8) proposed a hypothesis to explain the association between genital and renal anomalies in MRKH syndrome. Faulty gonadal differentiation can occur, with consequent production of Müllerian inhibiting factor, which induces regression of the Müllerian ducts, as normally seen in males. Depending on the onset of production of Müllerian inhibiting factor, and the asymmetry in production by the two gonads, the development of the Müllerian ducts would stop at various stages. This theory could explain the uterine asymmetry. In 16 of the 19 patients with unilateral renal anomalies, the uterine bud agenesis or fallopian tube dysplasia was ipsilateral; in the other three patients with unilateral urinary tract anomalies, the uterine bud agenesis or fallopian tube dysplasia was contralateral. This is variably reported by other authors (4, 7, 8, 10, 19).

All patients with associated ovarian abnormalities had type B MRKH syndrome. We agree with Ghirardini and Segre (9) that the hypothesis of Schmid-Tannwald and Hauser (8) could explain this association. This theory could also explain the inguinal hernia containing an ovary as was seen in six patients, because of the production of a male induction substance (8).

The theory of Schmid-Tannwald and Hauser is difficult to prove because biopsies of the ovaries were not performed in our patients and our study did not focus on detecting and isolating the Müllerian inhibiting factor. More studies need to be done, especially with respect to the ovaries, to confirm the suggestion of Schmid-Tannwald and Hauser that patients with type B MRKH syndrome may have a very slight form of female pseudohermaphroditism (8-10).

Review of the patient's medical history and a simple gynecologic examination usually are sufficient to diagnose MRKH (1, 4, 7). Laparoscopy was retrospectively reviewed in our study to differentiate between type A and type B of the disease. Sonography did not show differences between these two types when no urinary abnormality was shown. In those cases in which a diagnostic dilemma exists, sonography may be useful to confirm uterine agenesis (4, 20). In 6-10% of cases, however, endometrial tissue in the muscular buds or even a unicornuate uterus with hematometra may cause associated cyclic abdominal pain. Sonography has been recommended for diagnosis of these abnormalities (20, 21), which were seen in nine patients (10%) in our study. Four of these nine patients had a unicornuate uterus with a hematometra, which was correctly diagnosed on the basis of sonographic findings. In five other patients, sonograms did not show the small amount of endometrial tissue in the muscular buds, which was later found at laparotomy. The difficulties in detecting small remnants of endometrial tissue on sonograms has been reported (20).

In our study, all anomalies of the upper urinary tract were seen exclusively in patients with type B MRKH syndrome. Sonography provided the same information as excretory urography and provided additional information in cases of hematometra. We did not consider the role of MR imaging in discriminating between the two forms of MRKH syndrome in this study. It is not certain whether these two forms can be differentiated as accurately on MR images as at laparoscopy, but the recent study of Fidele et al. (22) might set a starting point. In small series of patients, MR imaging was useful for showing small amounts of endometrial tissue in patients who have cyclic abdominal pain (12, 22, 23). More prospective studies in representative groups of patients are needed to establish the definite role of MR imaging in patients with MRKH syndrome.

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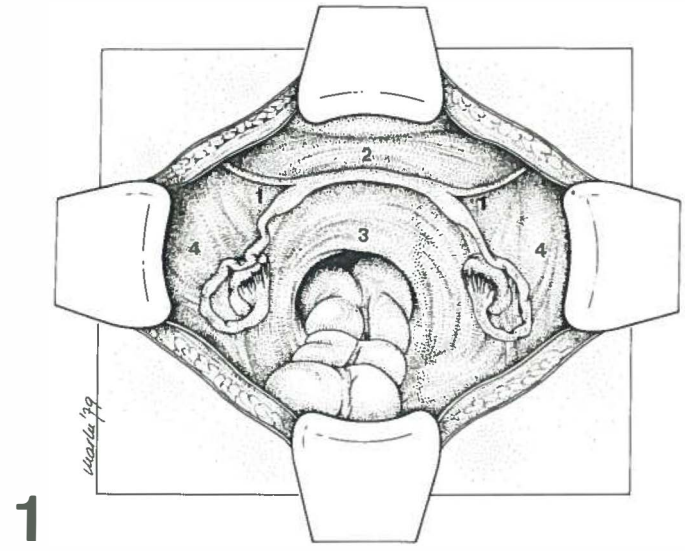

Fig. 1. Diagram shows characteristics of typical (type A) Mayer-Rokitansky-Küster-Hauser syndrome as seen at laparoscopy: symmetric muscular buds (1), absence of normal unterus (2), rectum (3), and normal fallopian tubes and ovaries (4).

Fig. 2. Laparoscopic view of patient with atypical (type B) Mayer-Rokitansky-Küster-Hauser syndrome shows right muscular bud (1), right fallopian tube (2), right ovary (3), and rectum (4). Although both ovaries were normal, patient had aplasia of left muscular bud and fallopian tube.

Chapter VII

HEARING LOSS AND THE MAYER-ROKITANSKY-KÜSTER-HAUSER SYNDROME

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VII.1 ABSTRACT

The hearing of 51 patients with the Mayer-Rokitansky-Küster-Hauser syndrome was examined using otoscopy and standard audiometry.

In 13 out of these 51 women (25.5%), a unilateral or bilateral hearing loss of ≥ 15 dB Fletcher Index was found. Four of these patients had a hearing loss of 20 dB in the worst ear. The remainder had a hearing loss of at least 30 dB in the worst ear.

Five out of the 13 women had pure conductive hearing loss. In four out of these five women, a congenital origin was accepted. Two women had mixed hearing loss which was a residual symptom from previous otitis media. Six women had sensorineural hearing loss. A congenital cause was found in one of these six women, based on the fact that she had been deaf and dumb since birth. In one other patient, noise-related deafness was likely (i.e. an acquired cause). In the other four cases in this group, the cause was unknown.

The results of this study show that hearing loss is a characteristic associated with the Mayer-Rokitansky-Küster-Hauser syndrome.

VII.2 INTRODUCTION

The Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is characterised by congenital aplasia of the vagina and uterus in women with a normal female phenotype and with anatomically and functionally normal ovaries (1-3). The incidence of this anomaly is estimated to be 1:4000 to 5000 (1, 3). In 30-40%, the MRKH syndrome is associated with congenital anomalies of the uropoietic tract and in 10-20% with congenital anomalies of the skeleton (1-5). This study reports on the hearing of 51 women with the MRKH syndrome.

VII.3 MATERIAL AND METHODS

This study was performed on 51 women with the MRKH syndrome, aged 19 to 45 years. They all had a normal chromosomal pattern. In retrospect, no indications of the MRKH syndrome could be found in the relatives of these women.

The average age was 26.4 years. Forty-nine of these women were patients at the University Hospital Nijmegen. One of them was from the University Hospital Groningen and one from the University Hospital Amsterdam. Owing to their special characteristics appropriate to the MURCS association, these two latter patients were invited to participate also in this study.

The women underwent a general ENT examination, in which special attention was paid to the presence of associated syndromal characteristics.

Otoscopy was conducted using a microscope. A standard audiogram was taken of all the women; in cases of (suspected) abnormalities, impedantimetry was performed. In 6 cases, existing ENT examination and hearing test results were used because the subject had died or did not wish to be re-examined.

The results of the hearing test are presented as the mean hearing loss at 500, 1000 and 2000 Hz (the so-called Fletcher Index). Abnormal hearing was defined as a hearing loss of ≥ 15 dB.

As hearing impairment and the MRKH syndrome can occur in combination with congenital anomalies of the uropoietic tract and the Klippel-Feil syndrome (congenital fusion of the cervical vertebrae), these structures were also examined in the hearing impaired women using intravenous pyelography and x-rays of the cervical vertebrae.

VII.4 RESULTS

In 13 out of the 51 women with the MRKH syndrome, a unilateral or bilateral hearing loss of ≥ 15 dB Fletcher Index was found (Table 2). Four women had a loss of 20 dB in the worst ear. In the remaining cases, the loss in the worst ear was at least 30 dB.

VII.4.a Conduction loss

A total of 5 out of the 13 women had a pure conductive hearing loss. Pure 60 dB hearing losses were seen in two women (nos 7 and 11, Table 1), with full bony atresia of the auditory canal in combination with microtia and hemifacial microsomia on the affected side (Fig. 1). One other woman had a unilateral conduction hearing loss of 60 dB (no. 8, Table 1) which had been present since childhood and was probably caused by an ossicular chain anomaly. Another woman with a conduction hearing loss of 30 dB (no. 5, Table 1), who appeared to have stapes ankylosis, was successfully operated on. Finally, one woman was found to have a conductive hearing loss of 15 dB (no. 4, Table 1), while the tympanic membrane on the affected side showed signs of scaring which was probably the result of earlier otitis media. In four out of these five cases, therefore, a congenital cause was accepted for the hearing loss.

VII.4.b Mixed hearing loss

Two women had a slight mixed hearing loss (nos 10 and 12, Table 1). Both cases had a poor otological history: one had recurrent otitis media with persistent otitis serosa, for which grommets had been inserted; the other woman had

chronic otitis media, for which tympanoplasty had been performed. On the basis of these findings, it is probable that the slight hearing loss was caused by otitis. A congenital cause is therefore considered unlikely.

VII.4.c Perceptive (sensorineural) hearing loss

Six women had a unilateral or bilateral sensorineural hearing loss. It was striking that in four cases (nos 1, 3, 9 and 13, Table 1), the loss was unilateral or asymmetrical, without any clear explanation. In two of these cases (nos 3 and 9), no conclusion could be drawn from the data as to whether or not the women were suffering from progressive perceptive hearing loss. Noise-related deafness was suspected in patient 9. For patient 13, a cochlear origin was established by means of tests, including electrocochleography and brain stem audiometry (Table 1). Patient 1 did not have progressive hearing loss. A retrocochlear pathology - a very rare disorder - could not always be excluded. We assumed that the persistent otitis on the affected side was the cause of the high-tone hearing loss. In one patient (no. 6, Table 1), a symmetrical dip-shaped perceptive hearing loss was found, very similar to that in autosomal dominant hereditary midfrequency deafness; however, her family history was negative. Another woman (no. 2, Table 1), had been suffering from bilateral total deafness since birth.

An overview of the above-mentioned results is shown in Table 3.

VII.4.d Association with other congenital anomalies

The Klippel-Feil (KF) syndrome was found to be an associated characteristic in 6 out of the 13 women with hearing loss (Table 2): the two with hemifacial microsomia (nos 7 and 11), the woman with congenital deafness (no. 2), the woman with asymmetrical mixed hearing loss (no. 12) and the two women with a congenital ossicular chain anomaly (nos 5 and 8).

An ectopic kidney or kidney agenesis was found to be an associated characteristic in 6 out of the 13 women (Table 2): one with hemifacial microsomia (no. 7), two with a congenital ossicular chain anomaly (nos 5 and 8), the woman with congenital deafness (no. 2) and two women with asymmetrical mixed hearing loss (nos 10 and 12).

The MURCS association (combination: kidney agenesis / ectopic kidney / KF syndrome / MRKH syndrome) was seen in 5 out of these 13 women (Table 2): the woman with congenital deafness (no. 2), the two women with a congenital ossicular chain anomaly (nos 5 and 8), one woman with hemifacial microsomia (no. 7; Fig. 1) and in one of the two women with the asymmetrical mixed hearing loss (no. 12). The concurrence of these associated anomalies supports the assumption that the hearing loss is of congenital origin and shows that there is an increased risk of hearing impairment in these patients.

VII.5 DISCUSSION

Only incidental reports have appeared on hearing impairment in patients with the MRKH syndrome (1-5). This study systematically examined the hearing of 51 women with the MRKH syndrome. Hearing loss was found in 13 of them. In 5 cases (5/51=10%), the cause was unmistakably a congenital anomaly of the ear. An acquired cause was probably responsible for the hearing loss in 4 women, whereas in the 4 remaining cases, it was not clear whether there was an acquired or a congenital cause for the hearing loss.

In this series, the women with a congenital hearing loss and the MRKH syndrome often also had other associated congenital anomalies. For example, 6 out of the 13 women with hearing loss had the Klippel-Feil syndrome [in 5 the hearing loss was congenital]. The association between hearing loss and the Klippel-Feil syndrome has been described before (2, 6-12). It has been reported that 30% of the patients with the Klippel-Feil syndrome also suffer from hearing loss (2, 6-9, 11). Wildervanck described the association between the Klippel-Feil syndrome, hearing loss and abducens paralysis, also referred to as the cervico-oculo-acoustic syndrome or the Wildervanck syndrome (6, 12-15). The majority of patients are female (6, 8). However, the association between the Klippel-Feil syndrome and congenital hearing loss is far more common without eye anomalies. None of our subjects had abducens paralysis. The cause is unknown. The hearing loss in combination with the Klippel-Feil syndrome can be perceptive, conductive or mixed (6, 8).

Very few reports have appeared in the literature on the association between the MRKH syndrome, the Klippel-Feil syndrome and a congenital anomaly of the ossicular chain. Park and Jones (2) described such as association in two unrelated women. This association was also seen in two of the subjects in our series (nos 5 and 8, Tables 1 and 2).

The association between congenital anomalies of the kidney and the ear has been reported more frequently (16-19) and is referred to as the Potter syndrome in the case of bilateral kidney agenesis (20). It was striking that all 3 women of Potter's study also had the MRKH syndrome. Abnormalities of the uropoietic tract have been described in 30-40% of the patients with the MRKH syndrome (1, 3). Several authors have also mentioned that a congenital conductive hearing loss can occur with this association (5, 20-21). In our series, 3 women had this combination of anomalies (nos 5, 7 and 8, Tables 1 and 2). It is interesting to note that Winter et al. (5), Turner (22) and King et al. (21) described families in which this combination of abnormalities was expressed in varying degrees. For McKusick (23), this formed the reason for presenting the possibility of separate pictures with an autosomal recessive or autosomal dominant hereditary pattern. Hemifacial microsomia was seen in 2 women in our series (nos 7 and 11, Tables 1 and 2). Hemifacial microsomia is sometimes so serious that the middle ear and the external auditory canal are improperly formed on the affected side (Figure

1). The hearing loss can also be caused by the inner ear and is sometimes bilateral (7). The association with skeletal and kidney anomalies has also been described.

The concurrence of the MRKH syndrome and hemifacial microsomia has only rarely been mentioned in the literature (3, 24). Winer-Muram et al. (24) described a congenital anomaly of the ossicular chain, together with the MRKH syndrome and hemifacial microsomia. In 1979, Duncan et al. (4) described an association of symptoms in 30 patients, for which the name the MURCS association was introduced. The MURCS association comprises the following components: aplasia of the tubes of Mueller (MU) (the MRKH syndrome), congenital kidney anomalies (Renal = R), cervical somite (CS) dysplasia (the KF syndrome); a combination with an increased incidence. In their patient group, the abnormalities were distributed as follows: MRKH syndrome (96%), kidney agenesis/ectopic kidney (86%), KF syndrome (80%). It was striking that 4 out of their 30 patients were hearing impaired, a finding which was mentioned without giving any further details. The MURCS association was seen in 5 of the women in our study group (nos 2, 5, 7, 8 and 12, Table 2; Fig. 1). Four of them had a congenital hearing loss: one with bilateral congenital deafness (n=1), two with an ossicular chain anomaly (n=2) and one with hemifacial microsomia with atresia of the external auditory canal (n=1). An acquired cause for the hearing loss was suspected in the fifth case (no. 12, Tables 1 and 2).

The MRKH syndrome, the Klippel-Feil syndrome, the renal anomalies, hemifacial microsomia and the congenital anomaly of the middle ear can occur as separate conditions. However, in some people they all occur together in varying degrees (2-5, 24). The question arises as to whether or not we are dealing with a coincidental concurrence. The data presented above show a fairly high prevalence of these associations. Therefore, it is not clear whether the MRKH syndrome is a separate syndrome with a separate cause, or whether it is an expression of the patients being affected in varying degrees with one or more underlying causes.

We do not yet know the answer to this question. But this study has shown that hearing loss is an associated characteristic of the MRKH syndrome. Moreover, if the anomaly is confined to the middle ear, it is possible to improve the patient's hearing using surgery (6).

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Table 1 Pure tone thresholds in patients with Hearing loss

Pat.no.	250 Hz		500 Hz		1'000 Hz		2'000 Hz		4'000 Hz		8'000 Hz		Additional information
	R	L	R	L	R	L	R	L	R	L	R	L	
1	10	10	10	10+5	5	0+5	10	40+0	0	45+0	0	40+0	Cochlear high tones, unilateral, non-progressive probably resulting from otitis media
2	>90	>90	>90	>90	>90	>90	>90	>90	>90	>90	>90	>90	Old pupil of an institute for the deaf
3	20	20	20	10+0	5	10+10	10	15+5	10	10+10	10	10+20	15 - 20 dB perceptive E.C.I.
4	15	30	10+5	10+0	0+15	5+10	5+5	20+10	0+10	15+10	10+0	15+10	15 dB Fletcher AS, E.C.I.
5	0+35	20	0+35	0+10	0+30	0+10	10+15	10+5	10+5	10+5	15+15	20+20	AD: Stapes ankylosis, successful surgery
6	45	40	30+25	30+10	45+20	50+10	60+0	60+0	70+0	70+0	70+0	60+0	Dip-shaped perceptive
7	15	>90	10	>90	5	>90	0	>90	20	>90	25	>90	Hemifacial microsomia, atresic external auditory canal
8	60	15	20+40	10	10+50	5	25+35	10	30+30	20	30+30	15	Congenital conductive 60 dB AD, ossicular chain anomaly
9	20	15	0+5	10+0	15+10	15+0	20+0	20+0	10+0	10+0	15+0	15+0	Perc. mid frequency Dip E.C.I., tympanic membrane normal
10	25	0+50	25+15	0+30	20+0	0+25	15	10	20	20+30	40	40+70	Recurrent otitis media bilat., grommets
11	10	15+45	5+15	20+50	10	20+55	5	20+55	5	20+55	10	20+55	Hemifacial microsomia, atresia external auditory canal
12	5+0	15+50	5+0	30+30	5+0	20+25	20+0	30+20	35+0	20+25	35+0	45	Chronic otitis media AS, with tympanoplasty
13	40	35	40+0	15+10	30+5	10+5	30+5	20+0	40+5	15+10	100	50	Asymmetrical cochlear hearing loss

Table 2 Main features in patients with the MRKH syndrome and hearing loss

Patient no.	Fletcher	Index	I.V.P.	Cervical Spine	Additional syndromal features
	R	L			
1	<15	20	N	N	-
2	>90	>90	L.P.K.	K.F.	MURCS association
3	<15	20	N	N	-
4	<15	15	N	N	-
5	30	<15	L.R.A.	K.F.	Stapes ankylose AD
6	60	50	N	N	-
7	<15	>90	L.P.K.	K.F.	MURCS association, Hemifaciale microsomia with atresia external Auditory canal L
8	60	<15	L.P.K. R.R.A.	K.F.	MURCS association, ossicular chain anomaly
9	20	15	N	N	-
10	25	20	R.R.H.	N	-
11	<15	70	N	K.F.	Hemifacial microsomia, with atresia external auditory canal L
12	<15	40	L.R.A.	K.F.	MURCS association
13	40	20	N	N	-

Abbreviations used in table 2:

L.P.K.	=	Left Pelvic Kidney
L.R.A.	=	Left Renal Agenesis
R.R.A.	=	Right Renal Agenesis
R.R.H.	=	Right Renal Hypoplasia
K.F.	=	Klippel-Feil Syndrome
N	=	Normal
-	=	No additional syndromal Features

Table 3:

	Congenital origin	Acquired	Unknown
Conductive loss	4 out of 5	1 out of 5	0 out of 5
Mixed loss	0 out of 2	2 out of 2	0 out of 2
Perceptive loss	1 out of 6	1 out of 6	4 out of 6
	5 out of 13	**4 out of 13**	**4 out of 13**

Figure 1:
A: frontal view, B: lateral view; C: X-ray of same patients as A and B, 10 years later.
Left-sided heifacial microsomia and microtia. Patient was found to have 60 dB pure conductive hearing loss caused by full bony altresia of the auditory canal in combination with the MURCS-association (see text).

Chapter VIII

THE MAYER-ROKITANSKY-KÜSTER-HAUSER (MRKH) SYNDROME WITHOUT AND WITH ASSOCIATED FEATURES: TWO SEPARATE SYNDROMES?

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VIII.1 ABSTRACT

A multidisciplinary study was conducted on a total of 100 women with the MRKH syndrome. During the course of the study it unexpectedly became possible to analyse whether the MRKH syndrome can be considered as a clinical entity or whether two or more syndromes lie behind the title 'the MRKH syndrome'.

Complete gynaecological and laparoscopical data were available on all of the patients to make this diagnosis. The patients were divided into two groups on the basis of the laparoscopical data: a typical and an atypical form of the MRKH syndrome.

We performed various diagnostic investigations to establish whether there were any associated congenital anomalies. These tests included general physical examination, X-rays of the vertebral column, the upper extremities and intravenous urography (IVU), and general otorhinolaryngological and ossicular chain examinations. Associated anomalies were most common in the group with the atypical form of the MRKH syndrome. These findings suggest that there might be two different syndromes in this patient group, namely an isolated form of congenital agenesis of the vagina and uterus and a more generalised form of a congenital syndrome, in which agenesis of the vagina and uterus is a major and perhaps even obligatory characteristic.

VIII.2 INTRODUCTION

In the Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, the vagina and uterus are absent (1-3). On the basis of laparoscopical findings, some authors have recently made a distinction between a typical and an atypical form of this syndrome (4-6). The typical form is characterised by symmetrical muscular buds and normal fallopian tubes. The atypical form shows asymmetrical uterine remnants (aplasia of one or both of the muscular buds, one bud smaller than the contralateral one) and/or abnormal fallopian tube development (aplasia/hypoplasia of one or both fallopian tubes).

In the framework of a multidisciplinary study on the MRKH syndrome, the initial step was to study 100 patients with the MRKH syndrome (6-9) and to pay particular attention to the presence of associated anomalies of the face, hearing, neck, kidneys and skeleton. The results indicated that a distinction could be made between a group of patients whose laparoscopical findings showed only the typical form of the MRKH syndrome without any other associated characteristics and a group whose laparoscopical findings showed an atypical form with one or more associated extragenital characteristics.

The aim of the present study on a group of 100 patients with congenital agenesis of the vagina and uterus, was to evaluate whether there is a correlation

between a laparoscopically typical or atypical form of the MRKH syndrome and the presence of associated extragenital characteristics.

VIII.3 MATERIAL AND METHODS

The results of the tests and the clinical data from 100 patients with the Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome were reviewed to identify any associated extragenital congenital anomalies. The age of the patients ranged from 15-45 years (mean: 23.9 years). Over an 11 year period (1980-1991), these patients were referred to the Department of Gynaecology and Obstetrics of the University Hospital Nijmegen, the Netherlands, because of primary amenorrhoea (80/100 = 80%), sterility (8/100 = 8%) or dyspareunia (12/100 = 12%). Based on the laparoscopical findings with regard to the internal genitalia, the 100 patients were classified as having the typical form or the atypical form of the MRKH syndrome. The typical form was characterized by symmetrical muscular buds and normal fallopian tubes. The atypical form showed asymmetrical uterine remnants (aplasia of one or both of the muscular buds, one bud smaller than the contralateral one) and/or abnormal fallopian tube development (aplasia/hypoplasia of one or both fallopian tubes).

In order to identify and further specify any (hidden) associated anomalies, the patients underwent the following radiological examinations: intravenous urography (n = 100), routine antero-posterior and lateral films of the cervical, thoracic and lumbar spines (n = 100), routine radiographs of the hand (n = 40). The intravenous urograms were reviewed for congenital urinary tract abnormalities, the spine studies for congenital spinal abnormalities, the radiographs of the hand also for congenital abnormalities (6-8).

Fifty-one patients were screened for hearing loss by standard tone audiometry, otoscopy and history. Hearing loss was classified as congenital, acquired or of unknown etiology (9).

The height of 92 patients was recorded in order to study any possible differences between patients with and without the associated extragenital abnormalities.

VIII.4 RESULTS

Based on the laparoscopical findings, 44 out of the 100 patients (44/100 = 44%) were diagnosed as having the typical form of the Mayer-Rokitansky-Küster-Hauser syndrome (MRKH syndrome), while the remaining 56 patients (56/100 = 56%) were diagnosed as having the atypical form. Extragenital anomalies were mainly found in the group with the atypical MRKH syndrome.

Table 1 presents the frequency of these extragenital features among the 56 patients with an atypical form of the MRKH syndrome, such as anomalies of the kidneys, spine, upper extremity, hand and other skeletal sites and hearing anomalies. It was remarkable that renal anomalies were present in 38 out of the 56 (68%) patients, while congenital spinal anomalies were seen in 39 out of 56 (70%) patients. In addition, 32 out of these 43 patients (74%) had anomalies of the arms and/or hands, while another 6 patients (11%) displayed other associated skeletal anomalies. Congenital hearing loss was diagnosed in at least 5 of the patients (9%). In 13 out of these 56 patients (23%) (Table 1) an association was found between a combination of a congenital renal anomaly and symptoms which could be interpreted as arising from dysplasia of the 'cervical somite'.

The extragenital anomalies found in the patients with the typical MRKH syndrome, mainly comprised anomalies of the spine and hand; they are listed in Table 2. In this group, it should be noted that there was not only a considerably lower frequency of skeletal anomalies, but also none of the patients had renal anomalies or congenital hearing loss.

The height of 92 of the 100 patients was measured. In the group with the typical form of the MRKH syndrome, the height ranged from 156-176 cm (mean 165 cm; N=39), while in the group with the atypical form, the height ranged from 144-178 cm (mean 163 cm; N=53). It can be concluded that in these patient groups, height does not form a characteristic which distinguishes patients with the atypical form from those with the typical form of the MRKH syndrome.

VIII.5 DISCUSSION

Although the MRKH syndrome is a fairly rare condition, it appears among the more frequent etiologies in the list of causes of primary amenorrhoea (3, 10, 11). There is no single, clear cause known for the MRKH syndrome. Earlier research has shown that on the basis of laparoscopical findings, a distinction can be made between a typical and an atypical form of the MRKH syndrome (4, 6). Moreover, it has been noticed that patients with the MRKH syndrome may also have other congenital anomalies, particularly of the kidneys and skeleton, such as the spine, arms, hands and face (1-4, 8, 10, 12-16).

In the framework of a multidisciplinary study on 100 women with the MRKH syndrome, we had a complete set of test results for nearly all of them (6-9). Only the hearing test results were available of 51 and the hand X-rays of 43 cases. Tables 1 and 2 show the frequency of the associated anomalies in the atypical and typical forms of the MRKH syndrome. The results indicate that in the atypical form of the MRKH syndrome, the genital anomalies form part of a more generalised series of physical symptoms. This could mean that the atypical form has a different etiology and that there are two nosologically distinguishable entities. The low frequency of associated anomalies of the spine and hands

shown in Table 2, might mean that these anomalies should have been classified under the atypical form of the MRKH syndrome, but that the laparoscopical method to differentiate between the two forms does not always suffice.

Although the nosologically unclear clinical picture of hemifacial microsomia (17) often seems to be associated with anomalies of the spine, kidneys and internal genitals, the MRKH syndrome appears to do the opposite.

It was striking that in a proportion of the patients, presented in Table 3, nearly all of the associated anomalies of the MRKH syndrome were present simultaneously. This observation emphasizes the opinion that there is something remarkable about the group of patients with an atypical form of the MRKH syndrome and has formed the reason why some authors have opted to classify this subgroup under 'the MURCS association' (18-21) (Figure 1). The letters MU stand for Müllerian duct dys/agenesis (the MRKH syndrome), the letter R for renal ectopia/agenesis and the letters CS for cervical somite dysplasia (the Klippel-Feil syndrome).

This is the first study in which a large number of patients were examined by a multidisciplinary team of specialists. Our observations strongly support the view that the recent tendency to differentiate between two forms of the MRKH syndrome on the basis of laparoscopical findings is justified and that it is very probable that there is an isolated form of congenital aplasia/dysplasia of the vagina and the uterus, and a generalised form of a congenital syndrome, in which aplasia/dysplasia of the vagina and uterus are a major and possibly even obligatory characteristic.

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Table 1: Extragenital abnormalities and the atypical form of the Mayer-Rokitansky-Küster-Hauser Syndrome (N=56)

Extragenital features	Number of features	Number of patients
Congenital abnormalities of the uropoietic tract:	43	38
- renal agenesis	24	
- renal ectopia / malrotation	16 (5 x combination with agenesis)	
- renal hypoplasia	3	
Congenital spinal abnormalities:	60	39
- Klippel-Feil (K.F.)	16	
- scoliosis	11 (9 x combination with K.F.)	
- sacralization L5	5	
- spina bifida occulta	25 (12 x combination with K.F.)	
- Fusion L2 / L3	1	
- sacral agenesis	2	
Upper extremity- / hand abnormalities:	35	35[x]
- radial aplasia	1	
- radial + scaphoid hypoplasia	4	
- arm agenesis	1	
- only measurable hand abnormalities*:	29	
Other skeletal abnormalities:	6	6
- facial asymmetry	3	
- Sprengel deformity	3	
Hearing Loss:	11	11[o]
- congenital:	5	
- stapes ankylosis	2	
- atresia of the acoustic canal	2	
- profound childhood deafness	1	
- acquired:	2	
- otitis media	2	
- unknown sensorineural hearing loss:	4	
MURCS-association[+]:	13	13

Abbreviations used in table 1:

*: Ref.nr. 8

+: MU = Müllerian duct dys/agenesis, R = renal ectopia/agenesis, CS = cervical somite dysplasia

x: 43 patients in all were studied for this item

o: 51 patients in all were studied for this item

Table 2:
Extragenital abnormalities and the typical form of the Mayer-Rokitansky-Küster-Hauser Syndrome (N=44)

Extragenital features	Number of patients
Congenital spinal abnormalities:	5
- sacralization L5	1
- spina bifida occulta	4
Only measurable hand abnormalities*:	7
Acquired hearing loss:	2

Abbreviations used in table 2:

*: Ref.nr. 8

Table 3:
The MURCS association and associated abnormalities (N=13)

	Number of patients
Hearing loss	5
Congenital:	4
- stapes ankylosis	2
- atresia of the acoustic canal	1
- profound childhood deafness	1
Acquired:	1
Upper extremity malformations:	3
- arm agenesis	1
- radial aplasia	1
- radial + scaphoid hypoplasia	1
Only measurable hand abnormalities*:	3
Facial asymmetry	2

Abbreviations used in table 3:

MURCS: see explanation used in table 1.
*: Ref.nr. 8

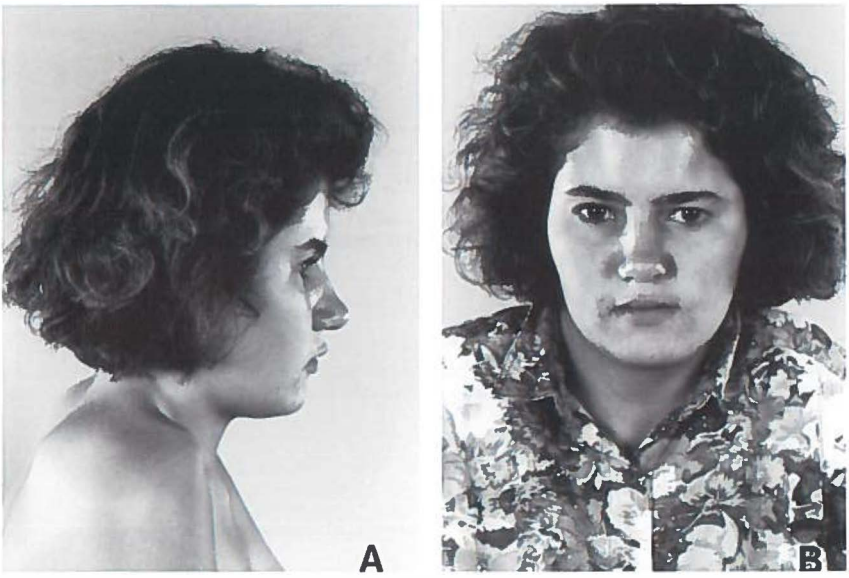

Figure 1

A: Lateral view, **B:** frontal view of a patient with the MURCS association.
The lateral view showes a short neck and low hairline caused by congenital fusion of cervical vertebrae i.e. the Klippel-Feil syndrome, which represents the „CS" in the MURCS association. The frontal view shows an associated facial asymmetry. This patient also proved to have congenital deafness caused by atresia of the external auditory canal, and renal agenesis, which represents the „R" in the MURCS association.

Laparoscopic findings showed the atypical form of the Mayer-Rokitansky-Küster-Hauser syndrome.

Chapter IX

SUMMARY OF RESULTS

IX.1 INTRODUCTION

The results of radiological and physical signs in the Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome are summarized in this chapter.

The findings of associated extragenital anomalies such as upper extremity (hand) abnormalities, spinal abnormalities, renal and ovarian desease and hearing loss, were related to the typical or the atypical form of the MRKH syndrome. The combination of the syndrome with abnormalities of the fallopian tubes (hypoplasia or aplasia of one or both tubes) and asymmetrical uterine remnants (aplasia of one or both muscular buds, and when both muscular buds were found, one muscular bud was larger with respect to the contralateral one) as diagnosed by laparoscopy was designated as the atypical form.

One hundred patients in all were studied. The atypical form was seen in 56 patients, the typical form in 44 patients.

In addition, because during our studies it became clear that all major extragenital features were found in the atypical group only, a study was undertaken to try to answer the question: the MRKH syndrome without and with associated features: two separate syndromes? This study included the MURCS association (Müllerian duct agenesis, renal anomalies and cervical spine dysplasia) in order to answer the question 5 of chapter I if this association is a separate entity or not.

IX.2 UPPER EXTREMITY- / HAND ABNORMALITIES

A systematic study of radiographs of the hands in 40 patients with the MRKH syndrome revealed a wide range of abnormal radiographic findings, varying from serious carpal and radial dysplasia in 3 patients to less severe abnormalities which could only be found by measuring. These patients had the following abnormalities: brachymesophalangy of digits 2-5, small distal phalanx of digit 1, long proximal phalanx of digits 3-4 and long metacarpals of digits 1-4.

Twenty-nine patients with only measurable anomalies were seen in the atypical group and only 7 of these patients were seen in the typical group.

In the overall group of 100 patients, 3 more patients with visible anomalies such as radial dysplasia, radial + scaphoid hypoplasia and arm agenesis were found. All 6 patients with distinct radial dysplasia and abnormalities of the carpals and the patient with arm agenesis proved to have the atypical form of the syndrome.

IX.3 VERTEBRAL COLUMN

The analysis of conventional antero-posterior and lateral films of the vertebral spine of the 100 patients in all with the MRKH syndrome revealed that the more severe congenital spinal abnormalities were seen only in 39 of the 56 patients with the atypical form of the MRKH syndrome. These 39 patients were found to have the following features: congenital fusion of cervical vertebrae [the Klippel-Feil (KF) syndrome] in 16 patients, scoliosis in 11 patients (9 x combination with KF), sacral agenesis in 2 patients, sacralization of L5 in 5 patients, spina bifida occulta in 25 patients (12 x combination with KF) and congenital fusion of L2-L3 in one patient.

Only in 5 of the 44 patients with the typical form of the MRKH syndrome more common spinal anomalies such as spina bifida occulta (4 cases) and sacralization of L5 (1 case) were found, with a remarkable lower incidence compared to the atypical group.

The most striking feature was the KF syndrome as part of the MURCS association as was found in 13 of the 16 patients with the KF syndrome.

The prevalence of spinal abnormalities was 44/100 (44%). For the atypical group only 39/56 (70%), for the typical group 5/44 (11%).

IX.4 RENAL ANOMALIES, OVARIAN DESEASE

The study of the excretory urographic findings of the 100 patients in all with the MRKH syndrome revealed anomalies of the urinary tract in 38 patients (38/100 = 38%), all of whom had the atypical form of the MRKH syndrome (38/56 = 68%). The renal abnormalities included: renal agenesis (24 cases), pelvic kidney (15 cases; 5 x combination with renal agenesis), renal hypoplasia (3 cases) and horseshoe kidney (1 case).

Laparoscopy in 91 patients showed additional abnormalities of the ovaries in 14 patients (14/91 = 15%), all of whom had the atypical form of the MRKH syndrome. These findings included: inguinal hernia containing an ovary (6 cases), no descent of ovary (5 cases), agenesis of one ovary (1 case) and streak ovaries (2 cases).

IX.5 HEARING LOSS

A study of 51 patients with the MRKH syndrome revealed hearing loss in 13 of them (13/51 = 25.5%). A congenital form with stapesankylosis, atresia of the acoustic canal or profound childhood deafness was diagnosed in 5 patients (5/51 = 9.8%), unknown sensorineural hearing loss in 4 patients (4/51 = 7.8%). In 3 of these latter patients a congenital form was suspected but not proven. The

acquired form, caused by noise damage or otitis media, was diagnosed in 4 patients (4/51 = 7.8%).

All patients with the congenital form and the unknown sensorineural form were seen in the group with the atypical form of the MRKH syndrome. Only 2 patients with the acquired form were seen in the group with the typical form of the MRKH syndrome. The MURCS association was seen in 5 patients, 4 of whom had congenital hearing loss.

IX.6 THE MURCS ASSOCIATION

A study of 100 patients with the MRKH syndrome revealed the MURCS association (Müllerian duct dys/agenesis, Renal ectopia/agenesis, Cervical somite dysplasia) in 13 patients. All these 13 patients proved to have the atypical form of the MRKH syndrome.

No significant difference in mean stature was seen between the typical group and the atypical group. No specific feature could be found in the MURCS association, which was not present in the atypical form of the MRKH syndrome.

IX.7 CONCLUSIONS

Question 1

Is subdivision of the MRKH syndrome into the typical and atypical form of value?

Discrimination between the typical and atypical form of the MRKH syndrome, based on anatomical differentiation by laparoscopy, is of significance since all serious extragenital features were found exclusively in the atypical group.

Question 2

Are upper extremity abnormalities, particularly of the hand, to be expected in patients with the MRKH syndrome?

Upper extremity abnormalities, particularly of the hand, are to be expected in patients with the MRKH syndrome. All 6 patients with serious anomalies were seen exclusively in the atypical group. Of the only measurable hand abnormalities in 36 patients, 29 were seen in the atypical group and 7 in the typical group.

Question 3

Which types of renal and spinal abnormalities are to be expected in the typical and atypical form of the MRKH syndrome respectively?

Renal abnormalities, of which renal agenesis and a pelvic kidney were the most common findings and spinal abnormalities, of which the Klippel-Feil syndrome, scoliosis and spina bifida occulta were the most common findings with a high incidence, were seen exclusively in the atypical form of the MRKH syndrome.

Question 4

Is additional audiometrical screening of value in patients with the MRKH syndrome?

Audiometrical screening in patients with the MRKH syndrome is of value since in 13/51 (25.5%) of the patients with this syndrome hearing loss was found. The audiometrical screening needs only to be done in the atypical group since congenital hearing loss was found as an associated characteristic in this group only.

Question 5

Is the MURCS association a separate entity?

The MURCS association is not a separate entity but part of the atypical form of the MRKH syndrome, since no specific features could be found in the MURCS association, which could not be found also in the atypical form of the MRKH syndrome.

In general it may be concluded that the atypical form of the MRKH syndrome needs to be differentiated from the typical form not only because of the anatomical differences found at laparoscopy such as fallopian tube anomaly and/or different muscular bud development and ovarian pathology, but also because of the high incidence of extragenital features such as renal agenesis/ectopia, serious spinal abnormalities (especially the KF syndrome and scoliosis), upper extremity anomalies and hearing loss. However, based on the results of chapter VIII it is justified to use the MRKH syndrome only in those patients who prove to have the typical form. In chapter VI it was discussed to use type A (typical form) and type B (atypical form) MRKH. However, the atypical form proved to be so general from head anomalies (hemifacial microsomia) till vagina, with the MURCS association as part of it, and with uterus and vagina agenesis as important and possible obligate sign, that it may be concluded that the atypical form has to be considered as a separate syndrome.

Chapter X

SUMMARY

The Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is a congenital syndrome in which the uterus and vagina are absent. Associated disorders mentioned in the literature include: Congenital renal disorders, congenital abnormalities of the vertebral column, congenital abnormalities of the upper extremities and hearing loss. Since 1979, a certain combination of symptoms has been recognized as a separate entity and is referred to as the MURCS association (MU = Müllerian duct aplasia/hypoplasia = the MRKH syndrome; R = renal agenesis/ectopia; and CS = cervical somite dysplasia = the Klippel-Feil syndrome).

The first intention of this thesis was to try to answer the question if it is worthwile to distinguish between the typical and atypical form of the MRKH syndrome. It proved possible to distinguish between these two forms using laparoscopy. The typical form was characterized by symmetrical nonfunctioning muscular buds (the Müllerian ducts remnants) and normal fallopian tubes, and the atypical form by aplasia of one or both buds, one bud smaller than the contralateral one, with or without dysplasia of one or both fallopian tubes.

The value of additional examinations was also studied. Finally a study was made to find out whether it is of significance to consider the MURCS association as a separate entity as has been common since 1979. Moreover in this study it was tried to answer the question: the MRKH syndrome without and with assiociated features: two separate syndromes?

Chapter I An overview is given of the MRKH syndrome, the associated abnormalities, the suggestion of the atypical form of the MRKH syndrome and the MURCS association.

The aim of the study is described as follows:

- To study in a representative group of patients whether a subdivision of the MRKH syndrome into the typical or atypical form, on the basis of anatomical differences, is of significance.
- Which associated abnormalities should be examined? Is there a difference with regard to the typical and atypical form?
- Is it relevant to regard the MURCS association as a separate entity?

Chapter II The gynecological aspects of the MRKH syndrome, the diagnostic procedures and the differential diagnosis are described in detail.

Chapter III The embryological aspects of the MRKH syndrome and associated abnormalities are discussed, including the

development of the urogenital tract, the vagina and gonads and some relevant embryological aspects of the skeleton.
The etiological aspects are also discussed in this chapter. As it is not possible to prove one sole cause, the usual theories on a teratogenic effect, genetic origin, limited medullary gonadal differentiation with consequent Müllerian inhibiting factor production and multifactorial genesis are described.

Chapter IV Standard radiographs of the hands were studied in 40 patients with the MRKH syndrome.
The anomalies observed ranged from serious carpal and radial abnormalities (N=3) to only measurable abnormalities. The following abnormalities could be measured in the majority of patients: Brachymesophalangy of digits 2-5 (N=22), small distal phalanx of digit 1 (N=22), long proximal phalanx of digits 3-4 (N=19) and long metacarpals of digits 1-4 (N=20). A pattern profile analysis was performed (i.e. a graph showing the difference in length with regard to the standard deviation from the normal value).
No characteristic graph was found of the MRKH syndrome. As was studied in chapter VIII, the serious carpal and radial abnormalities were seen exclusively in the atypical MRKH group. Twenty-nine patients with only measurable anomalies were seen in the atypical group, compared to 7 patients in the typical group. Our study showed that abnormalities of the hand, although not pathognomonic, can be expected in patients with the MRKH syndrome, especially in the atypical form.

Chapter V Standard radiographs of the spine in 96 patients with the MRKH syndrome were studied in order to assess the incidence of the Klippel-Feil (KF) syndrome (congenital fusion of cervical vertebrae) and the MURCS association and their combination with the typical or atypical form of the MRKH syndrome. Other spinal anomalies were also mentioned and related to the typical or atypical form.
The atypical form was seen in 52 patients (54.2%). Thirty-seven patients of this atypical group proved to have spinal anomalies (37/52 = 71.2%). All patients with the KF syndrome (14 cases) and the MURCS association (11 cases) were seen exclusively in this group. In the typical group only 5 patients with common spinal anomalies such as spina bifida occulta (4 cases) and sacralization of L5 (1 case) were seen.

This study showed that cervical spine films in patients with the MRKH syndrome are indicated only in the atypical form. In those cases where the MRKH syndrome is associated with the KF syndrome the MURCS association should be considered.

Chapter VI In 91 patients with the MRKH syndrome, the incidence and type of renal abnormalities which can be expected in the typical and atypical form of the syndrome were evaluated by means of excretory urograms. All patients were subjected to laparoscopy to discriminate between the typical and atypical form and to inspect the ovaries.
Thirty-four out of the 91 patients (37.4%) were found to have congenital anomalies of the urinary tract. The majority of these anomalies were renal agenesis and/or ectopia. All these anomalies were found exclusively in the atypical group.
Ovarian abnormalities were observed in 14 patients (15.4%). These abnormalities were also found exclusively in the atypical group. The results of our study showed that all associated renal and ovarian abnormalities occur only in the atypical form of the MRKH syndrome.

Chapter VII In 51 patients with the MRKH syndrome the hearing was examined using otoscopy and standard audiometry. In 13 patients, a hearing loss of ≥ 15 dB Fletcher Index was found. Four of these patients had a hearing loss of 20 dB in the worst ear. The remaining 9 patients had a hearing loss of at least 30 dB in the worst ear. In 5 of these patients, a congenital origin was accepted and in 4 patients the cause was unknown. In 3 of these latter 4 patients a congenital form was suspected but not proven. Our study showed that hearing loss is a characteristic associated with the MRKH syndrome. As was studied in chapter VIII, all patients with congenital hearing loss were found exclusively in the atypical group.

Chapter VIII One hundred patients, known with the MRKH syndrome, were studied to answer the question: the MRKH syndrome without and with associated features: two separate syndromes? This study included the MURCS association. The atypical form was found in 56 patients (56%). The MURCS association was seen in 13 patients (13/56 = 23%) who all had the atypical form of the MRKH syndrome. No specific feature could be found in the MURCS association, which was not present in the atypical form.

This study suggested two syndromes: the atypical form as a generalized syndrome with the MURCS association as part of it and with uterus and vagina agenesis as an important and possible obligate sign and the typical form as an isolated vagina and uterus agenesis.
In general: the MRKH syndrome should be used for the isolated form only.

Chapter X

SAMENVATTING

Het Mayer-Rokitansky-Küster-Hauser (MRKH) syndroom betreft patiënten bij wie aangeboren de baarmoeder en de vagina ontbreken.

In de literatuur beschreven geassocieerde afwijkingen zijn: aangeboren nierafwijkingen, aangeboren afwijkingen van de wervelkolom, aangeboren afwijkingen van de bovenste extremiteit en doofheid. Een bepaalde combinatie van verschijnselen wordt sinds 1979 als aparte eenheid onderkend en de MURCS associatie genoemd. MURCS is de afkorting voor: buizen van Müller a/hypoplasie = MU = het MRKH syndroom, renale anomalieën = R = nieragenesie/ectopie en cervicale somiet dysplasie = CS = het Klippel-Feil syndroom.

De eerste intentie van dit proefschrift was de vraag te beantwoorden of het zinvol is om een onderscheid te maken tussen de typische en de atypische vorm van het MRKH syndroom. Dit onderscheid bleek mogelijk op basis van een bij laparoscopisch onderzoek zichtbaar anatomisch verschil: de typische vorm werd gekarakteriseerd op basis van symmetrische niet funktionerende „muscular buds" (restanten van de buizen van Müller) en normale tubae. De atypische vorm werd gekarakteriseerd op basis van aplasie van één of beide „muscular buds", één „bud" kleiner dan de andere als ze beiden aanwezig waren, met of zonder tuba afwijking.

Vervolgens werd de waarde van aanvullende onderzoeken bestudeerd. Tenslotte werd een studie uitgevoerd om uit te zoeken of het van belang is de MURCS associatie als aparte entiteit te onderkennen, zoals dit sinds 1979 gebruikelijk is. Bovendien wordt in deze studie geprobeerd de vraag te beantwoorden of het MRKH syndroom zonder en met geassocieerde afwijkingen twee aparte syndromen zijn.

Hoofdstuk I Een overzicht wordt gegeven van het MRKH syndroom, de geassocieerde afwijkingen, de suggestie van de atypische vorm van het MRKH syndroom en de MURCS associatie.
Het doel van het onderzoek wordt als volgt aangegeven:

- nagaan in een representatieve patiëntengroep of onderverdeling van het MRKH syndroom in de typische en atypische vorm op basis van anatomische verschillen zin heeft.
- naar welke geassocieerde afwijkingen dient gezocht te worden? Is er een verschil ten opzichte van de typische en atypische vorm?
- is het relevant om de MURCS associatie als een aparte eenheid te beschouwen?

Hoofdstuk II De gynaecologische aspecten van het MRKH syndroom, de diagnostiek en de differentiaal-diagnostiek worden uitvoerig besproken.

Hoofdstuk III De embryologische aspecten van het MRKH syndroom en de geassocieerde afwijkingen worden besproken. Achtereenvolgens wordt ingegaan op de ontwikkeling van de tractus urogenitalis, de vagina en de gonaden, alsmede op relevante embryologische aspecten van het skelet.
Ook de etiologische aspecten worden in dit hoofdstuk besproken. Een oorzaak kan niet worden aangegeven. De gebruikelijke theorieën betreffende een teratogeen effect, een genetische oorsprong, een afwijkende medullaire gonadale differentiëring met als gevolg de produktie van Müllerian inhibiting factor en de multifactoriële genese worden besproken.

Hoofdstuk IV Standaard röntgenopnamen van de hand werden bestudeerd bij 40 patiënten met het MRKH syndroom.
De geconstateerde afwijkingen varieerden van ernstige carpale en radiale afwijkingen (N=3) tot alleen meetbare afwijkingen. De meeste patiënten hadden de volgende meetbare afwijkingen: brachymesophalangie 2e en 5e vinger (N= 22), een korte distale phalanx van de duim (N=22), lange proximale phalangen van de 3e-4e vinger (N=19) en lange metacarpalia van de 1e-4e vinger (N=20).
Een pattern profile analyse, een grafiek welke het verschil in lengte ten opzichte van de standaard deviatie van de normaalwaarde aangeeft, werd uitgevoerd.
Een karakteristieke grafiek van het MRKH syndroom werd niet gevonden. Uit de studie van hoofdstuk VIII werd duidelijk dat de ernstige radiale en carpale afwijkingen alleen geconstateerd werden in de atypische groep. Negenentwintig patiënten met alleen meetbare afwijkingen werden gezien in de atypische groep, tegenover 7 in de typische groep. Uit het onderzoek blijkt dat afwijkingen aan de handen, hoewel niet specifiek, te verwachten zijn bij patiënten met het MRKH syndroom, speciaal in de atypische vorm.

Hoofdstuk V Zesennegentig patiënten met het MRKH syndroom werden middels standaard röntgenopnamen van de gehele wervelkolom onderzocht om het voorkomen van het Klippel-Feil (KF) syndroom (een aangeboren vergroeing van cervicale wervels) en de MURCS associatie en hun associatie met de typische of atypische vorm van het MRKH syndroom. Andere wervelafwijkingen werden ook genoemd in relatie tot de typische of atypische vorm. De atypische vorm werd gezien bij

52 patiënten (54.2%). Zevenendertig patiënten van deze atypische groep bleken wervelafwijkingen te hebben (37/52 = 71.2%). Alle patiënten met het KF syndroom (14 gevallen) en de MURCS associatie (11 gevallen) werden uitsluitend in de atypische groep gezien. In de typische groep werden slechts 5 patiënten met geringe wervelafwijkingen gezien, te weten spina bifida occulta (4 gevallen) en sacralisatie van L5 (1 geval).
Deze studie toonde aan dat foto's van de cervicale wervelkolom alleen geindiceerd zijn in de atypische groep. In die gevallen waar het MRKH syndroom geassocieerd is met het KF syndroom moet de MURCS associatie overwogen worden.

Hoofdstuk VI Bij 91 patiënten met het MRKH syndroom is middels een intraveneus pyelogram (IVP) bestudeerd hoe vaak en welke nierafwijkingen voorkomen bij de typische en atypische vorm van het syndroom. Laparoscopie werd uitgevoerd bij alle patiënten om de indeling typische en atypische vorm te kunnen maken. Tevens is gekeken naar het macroscopisch effect van de ovaria.
Vierendertig van de 91 patiënten (37.4%) hadden congenitale afwijkingen van de urinewegen. Het grootste deel van deze afwijkingen bestond uit nieragenesie en/of bekkennier. Al deze afwijkingen werden uitsluitend in de atypische groep gezien. Veertien patiënten (15.4%) hadden afwijkingen van de ovaria. Deze afwijkingen werden eveneens uitsluitend waargenomen in de atypische groep. Uit de studie blijkt dat alle geassocieerde nier en ovarium afwijkingen alleen voorkomen in de atypische groep van het MRKH syndroom.

Hoofdstuk VII Het gehoor van 51 patiënten met het MRKH syndroom werd onderzocht middels otoscopie en standaard toonaudiometrie. Bij 13 patiënten werd een gehoorverlies geconstateerd van ≥ 15 dB Fletcher Index. Vier van deze patiënten hadden een gehoorverlies van 20 dB op het slechtste oor. De overige 9 patiënten hadden een gehoorverlies van minstens 30 dB op het slechtste oor. Bij 5 patiënten was er sprake van een congenitale oorzaak. Bij 4 patiënten bleef de oorzaak onbekend. Bij 3 van deze laatste 4 patiënten bestond een sterk vermoeden op een congenitale genese, dit kon echter niet bewezen worden. Uit de studie blijkt dat gehoorverlies een geassocieerd kenmerk is bij het MRKH syndroom. Zoals uit de latere studie, gepresenteerd in hoofdstuk VIII blijkt, werden alle patiënten met aangeboren gehoorverlies uitsluitend gezien in de atypische groep.

Hoofdstuk VIII Honderd patiënten, welke bekend zijn met het MRKH syndroom, werden bestudeerd om de vraag te beantwoorden of het MRKH syndroom zonder en met geassocieerde afwijkingen twee aparte syndromen zijn. In deze studie werd ook de MURCS associatie betrokken.

De atypische vorm werd gezien bij 56 patiënten (56%). De MURCS associatie werd gezien bij 13 patiënten (13/56 = 23%), deze patiënten hadden allemaal de atypische vorm. Geen specifiek kenmerk werd gezien in de MURCS associatie, welke niet aanwezig was in de atypische vorm.

De bevindingen suggereren dat binnen deze patiëntengroep sprake is van twee te onderscheiden syndromen te weten de atypische vorm als een gegeneraliseerd syndroom met de MURCS associatie als onderdeel daarvan en met vagina en uterusagenesie als belangrijk en mogelijk obligaat kenmerk. Daarnaast de typische vorm met een geisoleerde vagina en uterusagenesie.

In het algemeen zou kunnen worden gesteld dat het MRKH syndroom alleen nog gebruikt zou moeten worden voor de geisoleerde vorm.

Curriculum vitae:

1953	Born in Bilthoven, the Netherlands
1973	Leaving examination
1973-1975	Military service
1975-1983	Medical school, University of Groningen, the Netherlands
1983-1987	Resident in the department of radiology, University Hospital of Groningen, the Netherlands
1988	Consultant radiologist, department of radiology, Kristiansund, Norway
1988-1990	Fulltime staffmember, department of radiology, Academical Medical Centre, University of Amsterdam, the Netherlands
1989	Fellowship in skeletal radiology, San Diego, USA
1990-1992	Fulltime staffmember, department of radiology, Kantonsspital Bruderholz, Switzerland
1992-	Fulltime associated radiologist Rijnstate Hospital, Arnhem, the Netherlands